STUDIES ON NAPROXEN/NON-STEROIDAL ANTI-INFLAMMATORY DRUG TREATMENT: INFLUENCE OF DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS AND PATIENT AGE

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CHAPTER I

GENERAL INTRODUCTION AND PROBLEM STATEMENT

Introduction

The science studying the interactions between drugs and living systems, pharmacology, is conventionally divided into pharmacokinetics and pharmacodynamics. Pharmacokinetics concern absorption, distribution, biotransformation and excretion of a drug, and pharmacodynamics concern the effects or so-called pharmacological actions, be it therapeutic or toxic, of a drug. Useful drugs can produce powerful effects on living beings. Within the context of pharmacotherapy these effects are modified by factors which ensue from patient characteristics, e.g. irreversibility of lesions, and alterations in drug handling.

Clinical pharmacology comprises the scientific approach to the application of drugs with a proven or an expected therapeutic value in man.

Drug pharmacokinetics in patients need not correspond with data obtained in healthy young volunteers. Patients may share demographic or clinical characteristics that change drug disposition.Obviously, altered pharmacokinetics in a particular subgroup of patients can have serious consequences, e.g. the unforeseen occurrence of (lethal) adverse drug reactions in geriatric patients due to benoxaprofen accumulation[1]. Pharmacotherapy in the elderly often requires precautions in view of age-related changes in body composition, hepatic and kidney functions[2]. Especially regarding diminished renal function, there are many examples of altered drug pharmacokinetics[3]. Alterations of drug disposition may exist in other patients due to hampered metabolism in hepatic disease[4], or due to hypoalbuminaemia in the case of a highly albumin-bound drug[5].

Inflammatory diseases are associated with changes of a regulatory or an adaptive kind in organs and body fluids of patients, and these changes may influence the handling of drugs. Non-steroidal anti-

inflammatory drugs (NSAID) are applied in the symptomatic treatment of inflammatory joint diseases. These studies concerned the possible effects of the disease activity of rheumatoid arthritis and of patient age on naproxen pharmacokinetics. Furthermore, two side effects of NSAID were studied also in relation with age and disease activity: one well-known (gastrointestinal blood loss) and one suspected (congestive heart failure) side effect.

Choice of drug: naproxen

Naproxen [(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid][6] belongs to the group of 2-aryl propionic acid NSAID. The analgesic and anti-inflammatory properties of NSAID make these drugs the first choice in the pharmacotherapy of inflammatory locomotor diseases, with special emphasis on rheumatoid arthritis. The most probable mode of action of NSAID is by interference with prostaglandin synthesis at the site of inflammation[7,8]. The wealth of different NSAID available, without one proven superior drug, forces the prudent clinician to select a small number as tools to work with[9].

In chronic arthritis, anti-inflammatory therapy can be achieved with either 50 mg diclofenac sodium three times daily, 500 mg naproxen twice daily, 20 mg piroxicam once daily, or another NSAID in appropriate doses. The most important factor in the selection of the right drug for the right patient is the individual variability in response to different NSAID. A twice daily dosage regimen is convenient to the patient and may have the advantage that night pain and morning stiffness are covered in patients taking the second dose late in the evening. Naproxen is an often prescribed NSAID in the pharmacotherapy of arthritis[10,11].

From a pharmacological point of view it is important to note that the 2-aryl propionic acid NSAID, including naproxen, have a centre of asymmetry, raising two enantiomers with a mirror immage relationship. The two chiral forms differ in anti-inflammatory activity and in rate of metabolism. Chiral inversion of the inactive to the active enantiomer further complicates this matter, since pharmaceutical formulations of 2-aryl propionic acids NDAID, save naproxen, contain

a racemic mixture[12]. Naproxen formulations contain only the active (+) enantiomer. Pharmacokinetic studies of racemates, being mixtures of two or more pharmacologically active compounds, without an attempt to separate the contribution of the individual stereoisomers or even without a notice on the very phenomenon, are dissuaded[13].

Earlier studies suggested that naproxen-albumin binding is an important determinant of naproxen pharmacokinetics[14]. In volunteers, the intake of increasing doses of naproxen did not lead to a linear growth of the area under the concentration-time curve (AUC). Non-linear, decreasing increments of AUC have been observed upon administration of increasing doses[15,16], probably due to increased clearance of the drug resulting from saturation of protein binding. For the study of the consequences of naproxen-albumin binding, measurements of protein-unbound drug concentrations are necessary.

Choice of disease: rheumatoid arthritis

Rheumatoid arthritis is defined by the criteria of the American Rheumatism Association[17]. In patients with rheumatoid joint inflammation, the indication for long-term treatment with one of the NSAID is evident. The disease runs a chronic, fluctuating course, with active periods of polyarticular inflammation relieved by periods of remission. The disease activity of rheumatoid arthritis has a variable expression in individual patients and can be assessed on the basis of clinical and biochemical findings[18,19]. Relevant clinical findings include a count of the number of swollen, tender and painful joints, estimation of the duration of morning stiffness and a search for extra-articular manifestations of the disease. Laboratory findings comprise the erythrocyte sedimentation rate, haemoglobin concentration and C-reactive protein. In relation with naproxen pharmacokinetics it is of importance to note that active disease is associated with hypoalbuminaemia [20,21]. The change from active disease to remission in a patient within a certain period of time allows the investigator to study naproxen pharmacokinetics separately in these two conditions in one patient. Patients with classic rheumatoid arthritis in a period of active polyarticular inflammation

were therefore selected for this study.
Active or progressive joint inflammation warrants, apart from NSAID therapy, treatment with a remission-inducing agent, i.e. hydroxychloroquine, aurothioglucose or d-penicillamine. Individualization of pharmacotherapy is required, and in the study population of patients with active rheumatoid arthritis co-medication could therefore not be standardized. Interference of such and other co-medication with naproxen pharmacokinetics could not be excluded completely, but it was avoided where possible.

PROBLEM STATEMENTS

Naproxen pharmacokinetics in patients with rheumatoid arthritis during active polyarticular inflammation (Chapter II)
Naproxen pharmacokinetics in healthy volunteers are well-known[22]. Differences exist between young healthy volunteers and patients with rheumatoid arthritis: e.g. age, the preponderance of women with arthritis and the presence of a generalized inflammation. These may contribute to alterations in naproxen pharmacokinetics in patients. It was expected that the lower serum albumin concentration in patients would influence the volume of distribution and total body clearance of the highly albumin-bound drug by exceeding the binding capacity at a lower serum naproxen concentration. Changes in clearance of protein-unbound drug might reflect the influences of disease activity on drug metabolism and were therefore studied by measurements of unbound naproxen concentrations. A pharmacokinetic study was performed in 8 patients with active polyarticular inflammation of rheumatoid arthritis and 8 healthy young male volunteers, during chronic treatment with oral naproxen 500 mg twice daily.

Naproxen pharmacokinetics in elderly patients (Chapter III)
Data on naproxen pharmacokinetics in young and elderly healthy male volunteers during chronic intake of 375 mg naproxen twice daily have been published[23]. A 50% reduction of the protein-unbound drug

clearance was found, together with a doubling of the unbound drug fraction; the latter pointing to diminished serum albumin binding. This resulted in total drug concentrations and total body clearances of naproxen which were indistinguishable from those in the young. Another study compared naproxen pharmacokinetics in elderly patients with results in middle-aged patients[24]. We performed a study of naproxen pharmacokinetics in male and female elderly patients with 500 mg oral naproxen twice daily and compared the results with data obtained in young healthy volunteers. Our study adds further data to current knowledge, because it compares elderly patients with healthy young volunteers after multiple high dosages.

Disease activity of rheumatoid arthritis and naproxen pharmacokinetics: a within-patient study (Chapter IV and V)

A within-patient study was performed on naproxen pharmacokinetics in rheumatoid arthritis at the time of active polyarticular inflammation compared with a period of major improvement in disease activity. A total of 16 potential subjects entered the study during the period from December 1984 to July 1986. Ten of these attained major improvement, nearly or completely fulfilling the criteria of complete remission[25] in rheumatoid arthritis at some time during the study period until January 1987. Of the ten eligible patients, two refused cooperation with a second investigation of naproxen pharmacokinetics. Both gave a similar reason for their refusal, no longer feeling the need for NSAID medication at a rather high dosage. One other patient did not comply with the protocol. In one patient acenocoumarol therapy had been started some time after the first investigation; this prevented a second study. Thus six patients remained, in whom the study was completed. One of these six is described separately (Chapter V).

Gastrointestinal blood loss during treatment with naproxen for rheumatoid arthritis (Chapter VI)

Recent studies show both a significant risk of upper gastrointestinal tract bleeding associated with NSAID exposure in the population[26]

and a significantly more frequent use of NSAID in those admitted to hospital with a bleeding peptic ulcer[27]. NSAID damage the gastrointestinal tract mucosa at least partly as a consequence of inhibition of local prostaglandin synthesis[28]. Subjective symptoms do not correlate with the presence of endoscopic lesions[29] and abdominal pain is an infrequent presenting complaint of gastrointestinal bleeding due to NSAID[30]. A quantitative estimate of the daily faecal blood loss can be obtained by the method of reinfused ^{51}Cr-labelled autologous erythrocytes. We studied gastrointestinal blood loss in 9 patients with active rheumatoid arthritis on chronic, well-tolerated therapy with 500 mg oral naproxen twice daily to look for a possible correlation with total or unbound drug concentrations or the degree of disease activity.

Congestive heart failure due to non-steroidal anti-inflammatory drugs in the elderly (Chapter VII)

NSAID in common use today can be the cause of solute retention[31]. Furthermore, NSAID may attenuate the effects of diuretics[32]. The possibility of inducing congestive heart failure by instituting NSAID therapy in the aged, therefore, merits attention. Chapter VII describes the results of an attempt to assess the probability of this suspected adverse drug reaction. Data were collected by means of a questionnaire to practicing physicians, participants of a post-graduate course on locomotor diseases in the elderly, and by analysis of the medical records of 600 patients with congestive heart failure in the Department of Medicine at the University Hospital St Radboud. This approach was based on the supposition that frequent occurrence of the presumed side effect should make it possible to locate at least some evident cases by inquiry, or within a number of 600 available patients with congestive heart failure. The results of this study are presented in Chapter VII.

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CHAPTER II

NAPROXEN PHARMACOKINETICS IN PATIENTS WITH RHEUMATOID ARTHRITIS DURING ACTIVE POLYARTICULAR INFLAMMATION

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Naproxen pharmacokinetics in patients with rheumatoid arthritis during active polyarticular inflammation

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1 Patients with rheumatoid arthritis often have hypoalbuminaemia as a sign of disease activity. In view of the extensive binding of naproxen to albumin, the pharmacokinetics of total and unbound drug were studied in eight patients and eight healthy male volunteers during chronic intake of 500 mg twice daily.

2 The area under the serum concentration-time curve of total naproxen during a dose interval, AUC (0,12), was smaller in patients (641 ± 101 mg l^{-1} h) than in volunteers (896 ± 85 mg l^{-1} h; $P < 0.0001$). The unbound naproxen AUCu (0,12) was larger in patients (1.9 ± 0.9 mg l^{-1} h) than in volunteers (0.7 ± 0.2 mg l^{-1} h; $P < 0.01$).

3 The higher unbound naproxen concentrations in patients were accompanied by an approxmately 40% increase in apparent clearance/bioavailability (CL/*F*) and a 60% increase in volume of distribution (*V*/*F*).

4 Both CL/*F* and *V*/*F* were inversely correlated with the individual serum albumin concentration ($r = -0.76$, $P < 0.001$; $r = -0.85$, $P < 0.001$, respectively)

5 The high unbound naproxen concentration in the serum of patients with active rheumatoid arthritis and concomitant hypoalbuminaemia is not known to be accompanied by an increase in side effects and may be beneficial if anti-inflammatory effects correlate with unbound drug concentration.

Keywords clinical pharmacokinetics naproxen rheumatoid arthritis hypoalbuminaemia

Introduction

In patients with active rheumatoid arthritis general signs of inflammation are often present, one of the features being a low serum albumin concentration (Baum & Ziff, 1985) The pharmacokinetics of highly albumin bound drugs, such as naproxen, can be expected to differ from normal in patients with hypoalbuminaemia (Koch-Weser & Sellers, 1976; Rowland, 1984). Therefore we studied naproxen pharmacokinetics during chronic therapy at a dosage of 500 mg twice daily in eight patients with rheumatoid arthritis in an active phase of the disease, and compared the results with values obtained in eight healthy male volunteers.

Methods

Eight in-patients, aged 62 ± 3 years (mean ± s.d), with either classical or definite rheumatoid arthritis according to the criteria of the American Rheumatism Association (Ropes *et al.*, 1958),

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entered the study. The individual values of clinical and laboratory parameters to assess disease activity in each patient and medication data are shown in Table 1. All patients had been taking naproxen 500 mg twice daily (Naprosyne®, tabl. 250 mg, Sarva-Syntex Nederland, Rijswijk, The Netherlands) for at least 14 days before the study. On the day of study the morning dose of any medication other than naproxen was either omitted or postponed until noon. Naproxen 500 mg was given with breakfast. Immediately before ingestion of the drug an indwelling catheter was placed in an antecubital vein and a sample of blood was drawn at time t_0. Further samples were taken 0.5, 1, 1.5, 2, 3, 4, 8, and 12 h after t_0. During this period the freely voided urine was collected. The mean endogenous creatinine clearance was 85 ± 22 ml min^{-1}; a normal value for the age of the patients (Siersbaek Nielsen *et al.*, 1971). The mean serum albumin concentration was 28 ± 2 g l^{-1}. This was measured by the bromocresolgreen method according to Doumas *et al* (1971). Serum and urine samples were stored at −20° C until analysis.

Eight healthy male volunteers, aged 24 ± 3 years, with a mean serum albumin concentration of 45 ± 2 g l^{-1}, entered the study. They had not taken any drug during at least 1 month preceding the study and no drug intake other than naproxen was allowed.

Naproxen 500 mg was administered twice daily at 08.30 h and 20.30 h. The morning dose of the drug was taken with breakfast. On the fourth day of naproxen intake blood samples were taken and urine collected, as described for the patients.

Measurement of naproxen in samples of serum and urine was by high pressure liquid chromatography and spectrofluorophotometric detection: the coefficient of variation for total serum naproxen (concentration range 20 – 120 mg l^{-1}) was 1.2% (Van Loenhout *et al.*, 1982). The unbound naproxen serum concentration in the samples was determined after equilibrium dialysis at 37° C for 5.5 h against isotonic Sorensen phosphate buffered saline, pH 7.4. The dialysis cell contained 1 ml serum and 1 ml buffer, separated by a cellulose dialysis membrane (Cuprophane M150). Adsorption of the drug to the membrane was negligible. The coefficient of variation over the concentration range 0.03 – 0.3 mg l^{-1} was 4.2%. The area under the concentration-time curve during a dose interval of 12 h, AUC (0,12), was estimated using the linear trapezoidal rule. Total body clearance/bioavailability (CL/*F*) was calculated as: dose (500 mg)/AUC (0,12) and expressed in ml min^{-1} or l min^{-1}. The elimination rate constant (λ) was obtained from the slope of the log-linear regression line through the last three time points in the dose interval. The elimination half-life $t_{½}$ was calculated from λ^{-1}·0.693. An apparent volume of distribution (*V*/*F*), corrected for individual body weight, was calculated from $CL/F\lambda^{-1}$ divided by the individual body weight From the values of unbound serum naproxen concentrations identical calculations were performed to obtain the pharmacokinetic parameters for unbound naproxen: AUCu (0,12), CLu/*F*, $t_{½}$u and *V*u/*F*.

Statistical analysis

The means of the pharmacokinetic parameters in both groups were analysed for statistically significant differences with the two tailed *t*-test

Table 1 Measures of disease activity and drug therapy in eight patients with active rheumatoid arthritis during chronic therapy with naproxen 500 mg twice daily

Patients *Age (years)*	*Sex*	*Hgb* (g/dl)*	*ESR† (mm h^{-1})*	*Morning stiffness (h)*	*Number of swollen joints*	*Number of tender joints*	*Comedication‡*
60	F	8 5	113	1	25	4	1.2
64	F	9 7	129	0.5	17	10	1.3
63	M	9 8	88	0	7	7	1.3
65	M	11 1	116	1	10	17	1.4 5 6.
55	F	11.0	56	1 5	13	6	1.5.7
63	F	9 9	77	0	9	9	1.5
65	F	9 9	80	2	9	5	8
61	F	8 5	80	2.5	28	30	8.9

* Hgb haemoglobin normal values M 14–18 g/dl; F 12–16 g/dl

† ESR erythrocyte sedimentation rate (Westergren) normal value F < 21 mm h^{-1}; M < 10 mm h^{-1}

‡ Comedication 1 aurothioglucose, 2 oxazepam, 3 cimetidine, 4. alprenolol, 5 ferrous fumarate, 6 temazepam, 7 frusemide, 8 azathioprine, 9 prednisone.

for unpaired data Results were expressed as mean ± s d unless otherwise stated

Study ethics

The study was approved by the ethics committee of the University Hospital St Radboud Patients gave verbal and volunteers written informed consent

Results

The pharmacokinetic data of naproxen during chronic intake of 500 mg twice daily both for patients with active rheumatoid arthritis and the healthy male volunteers are listed in Table 2 The mean total and unbound serum naproxen concentration-time curves for patients with active rheumatoid arthritis and healthy male volunteers are shown in Figure 1 The serum naproxen concentrations at time 0 (C_{min}) and peak (C_{max}) were significantly lower in patients than in healthy volunteers (both $P < 0.0001$), also the AUC (0,12) was smaller in patients 641 ± 101 mg l^{-1} h *vs* 896 ± 85 mg l^{-1} h ($P < 0.0001$) In the patient group there was a significantly larger V/F and CL/F, whereas $t_{\frac{1}{2}}$ was not different from that in the group of healthy volunteers The unbound naproxen concentrations at C_{min} and C_{max} were significantly higher in patients than in healthy volunteers ($P < 0.02$ and $P < 0.01$ respectively), also the AUCu (0,12) was found to be greater 1 9 ± 0 9 mg l^{-1} h *vs* 0 7 ± 0 2 mg l^{-1} h ($P < 0.01$) The values of CLu/F and Vu/F were significantly smaller in patients with active disease than in volunteers (both $P < 0.001$).

The values of V/F in both groups were negatively correlated with serum albumin concentration

Table 2 Pharmacokinetics (mean ± s d) of naproxen in eight patients with active rheumatoid arthritis and eight healthy male volunteers during chronic intake of naproxen 500 mg twice daily

		Total serum naproxen			*Unbound serum naproxen*		
		Patients	*Volunteers*	P	*Patients*	*Volunteers*	P
C_{max}	(mg l^{-1})	79 ± 12	110 ± 7	< 0 0001	0 42 ± 0 21	0 19 ± 0 07	< 0 02
C_{min}	(mg l^{-1})	38 ± 8	57 ± 7	< 0 0001	0 07 ± 0 02	0 03 ± 0 01	< 0 01
AUC (0.12)	(mg l^{-1} h)	641 ± 101	896 ± 85	< 0 0001	1 9 ± 0 9	0 7 ± 0 2	< 0 01
CL/F	(ml min^{-1})	13 3 ± 2 5	9 4 ± 0 9	< 0 001			
	(l min^{-1})				5 3 ± 2 5	11 9 ± 2 7	< 0 001
V/F	(l kg^{-1})	0 18 ± 0 03	0 11 ± 0 01	< 0 0001	26 ± 13	72 ± 27	< 0 001
$t_{\frac{1}{2}}$	(h)	10 4 ± 2 0	10 0 ± 1 8	NS	3 6 ± 0 8	4 8 ± 0 8	< 0 02

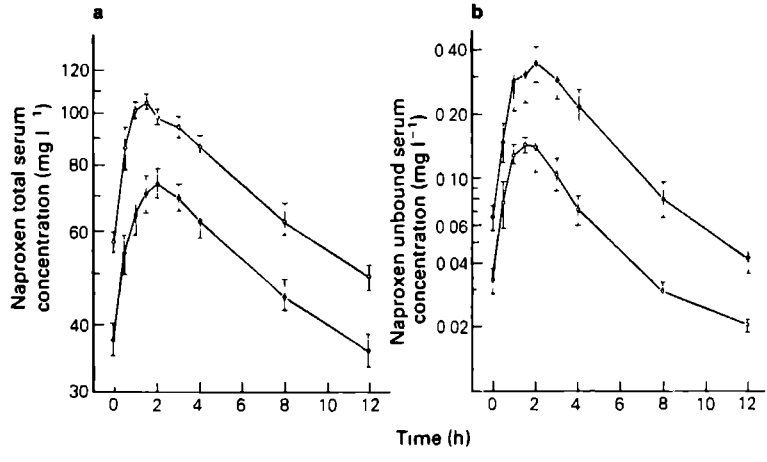

Figure 1 Serum naproxen concentration-time curves in eight patients with active rheumatoid arthritis (●) and eight healthy male volunteers (○) for total (a) and unbound drug (b) over one dose interval during chronic intake of 500 mg naproxen twice daily Bars indicate the s e mean

($r = -0.85$, $P < 0.001$) The values of CL/F in both groups were also inversely correlated with serum albumin concentration ($r = -0.76$, $P < 0.001$)

The recovery of naproxen and desmethylnaproxen conjugates, excreted in the urine during the 12 h dose interval was similar in the patients and the volunteers (1.2 ± 0.2 mmol and 1.3 ± 0.1 mmol naproxen equivalents, respectively) These values represented 54% and 59% of the oral naproxen dose during chronic intake in patients and volunteers, respectively

Discussion

In the group of eight patients with active rheumatoid arthritis the value of AUC (0,12) was 72% that in eight healthy male volunteers during one dose interval of 12 h on chronic treatment with naproxen 500 mg twice daily All subjects took the morning dose of 500 mg with breakfast, which is known not to interfere with the completeness of drug absorption (Segre, 1975) Any other medication in the patient group was either omitted or given at a later time to avoid a possible interaction with naproxen absorption In healthy volunteers naproxen absorption after oral administration of a single dose up to 4000 mg is nearly complete However, non-linear, decreasing increments of AUC have been observed upon administration of subsequent larger doses, probably due to saturation of albumin binding (Runkel *et al* , 1974, 1976)

The similar renal excretion of drug equivalents in patients and volunteers in this study suggests an unchanged absorption of the drug in patients. For these reasons it is concluded that the smaller AUC (0,12) values in patients with rheumatoid arthritis were not the consequence of impaired absorption of naproxen in active disease

The alterations of AUC (0,12), *V/F* and CL/*F* found in patients with active rheumatoid arthritis during chronic naproxen treatment are consistent with the pharmacokinetics of comparable compounds The clearance of drugs with high albumin binding and a low extraction ratio is affected by changes in the unbound drug fraction, and an increase in the concentration of unbound drug thus results in a higher total clearance (Rowland, 1984) Both *V/F* and CL/F in the patients with active disease were 40–60% higher than the corresponding values in healthy volunteers Therefore, with regard to the equation $t_{\frac{1}{2}} = 0.693\ V/CL$, little difference in $t_{\frac{1}{2}}$ between the two groups is expected

The clinical consequences of higher unbound concentrations of naproxen in patients with active rheumatoid arthritis are unclear In general, increases in unbound drug may change a therapeutic concentration into a toxic one Data on the possible relation of the occurrence of side effects in patients with high unbound naproxen concentration are not available Neither the incidence nor the severity of side effects has so far been found to increase during treatment of patients with rheumatoid arthritis with dosages as high as 1500 mg naproxen daily (Day *et al* , 1982, Hazleman *et al* , 1979, Mowat *et al* , 1984)

On the other hand, the increase in unbound naproxen concentration especially in patients with more active disease might be beneficial if the anti-inflammatory effects of naproxen correlate with unbound drug concentration in the serum

The differences found in CLu/*F* and *Vu*/F between patients and healthy volunteers may result from multiple causes e g age, differences in sex distribution, and in the existence of rheumatoid arthritis Upton *et al* (1984) observed in elderly males (mean age 71 ± 4 years) during long-term naproxen administration a decrease by more than 50% of CLu/*F* compared with young males (29 ± 6 years), and also in the elderly a rise in unbound naproxen plasma concentrations A similar difference in age exists between the patients (62 ± 3 years) and volunteers (24 ± 3 years) in this study Apart from the age-related factors, disease activity in patients with rheumatoid arthritis may have implications The same group of patients will be re-examined as soon as a remission of rheumatoid arthritis or a major improvement in disease activity has been achieved to study disease-related changes in naproxen pharmacokinetics

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CHAPTER III

PHARMACOKINETICS OF HIGH-DOSAGE NAPROXEN IN ELDERLY PATIENTS

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(submitted for publication)

SUMMARY

- After multiple oral doses of 500 mg naproxen twice daily, eight young healthy male volunteers and six male and female elderly patients participated in a pharmacokinetic study.
- Serum naproxen levels were measured by high-pressure liquid chromatography; protein-unbound drug was determined after equilibrium dialysis.
- A significantly lower maximal serum concentration (C_{peak}), smaller area under the curve during one dose interval [AUC(0-12)], larger total body clearance (CL/F) and apparent volume of distribution (V/F.Body Weight^{-1}) were found for the total drug in elderly patients.
- The pharmacokinetics of the protein-unbound drug showed higher trough and peak concentrations, larger $AUC(0\text{-}12)_u$, and smaller $(CL/F)_u$ and $(V/F)_u$ in the elderly patients.
- The unbound fraction (<1% of total naproxen) showed concentration dependency; in the elderly a larger unbound fraction was found.
- Pharmacokinetic differences between the elderly and the young may be explained by a lower serum albumin concentration in the aged, together with a decrement in binding affinity of naproxen to albumin; moreover, the clearance of unbound drug was significantly reduced in the elderly (281 ± 96 l/h) as compared with the young (713 ± 164 l/h).
- We conclude that age-related factors increase serum unbound naproxen concentrations. It is therefore advisable to start treatment with naproxen in the elderly at a low dosage.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAID) are frequently prescribed in rheumatoid arthritis and osteoarthritis. Some NSAID have long been available and tend to be given in larger doses even in the treatment of elderly patients. It is therefore important to study the pharmacokinetics of NSAID in the elderly during long-term administration of realistic, i.e. large doses as used today. We performed a pharmacokinetic multiple dose study with 500 mg oral

naproxen twice daily in elderly patients and compared the results with those obtained in young healthy volunteers.

METHODS

Six elderly male (n=2) and female (n=4) patients were studied. Eight young male volunteers, found healthy at examination and not taking medication in the preceding month, were given 500 mg naproxen twice daily for four days in the form of tablets of 250 mg (Naprosyne^{R}, Sarva Syntex Nederland, Rijswijk, The Netherlands). The patients had been treated with 500 mg naproxen twice daily in identical tablets for at least two weeks, in view of osteoarthritis (n=4) or rheumatoid arthritis (n=2). Characteristics of the groups are listed in Table I.

TABLE I. CHARACTERISTICS OF YOUNG VOLUNTEERS AND ELDERLY PATIENTS (mean ± SD)

		YOUNG (n=8)	ELDERLY (n=6)	p
age	(years)	24 ± 2.5	73 ± 2.9	<0.001
height	(cm)	185 ± 9	165 ± 6	<0.001
weight	(kg)	71 ± 11	60 ± 13	NS
serum creatinine	(μmol/l)	83 ± 11	71 ± 10	NS
creatinine clearance	(ml/min)	135 ± 12	66 ± 18	<0.001
serum albumin	(g/l)	45 ± 2	34 ± 5	<0.001

Kidney function was estimated in volunteers by determination of endogenous creatinine clearance from 24 hour urinary excretion and serum concentration; and in the elderly patients by means of a nomogram using the variables age, body weight, gender and serum creatinine concentration (Siersbaeck-Nielsen et al., 1971). Serum albumin concentration was measured by the bromocresolgreen method according to Doumas et al. (1971); reference value: 37-47 g/l. The serum albumin concentration in the elderly was significantly lower

than that in the young ($p<0.001$) and ranged from 28 to 42 g/l. Hypoalbuminaemia in elderly patients was not caused by hepatic failure, proteinuria, malnutrition or enteropathy.

In the aged, co-medication was not discontinued: it comprised 10 mg prednisone and 75 mg azathioprine in one patient, 400 mg hydroxychloroquine sulphate in one patient and 40 mg furosemide in one patient. On the day of study the co-medication was administered at least two hours after ingestion of naproxen. For volunteers no drug intake other than naproxen was allowed during the study period. On the day of study all subjects received 500 mg naproxen orally with breakfast after an overnight fast.

Study design

Before ingestion of the drug (time 0), and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours thereafter, blood samples were collected from a forearm vein. In the patients the sampling points 1.5 and 3 hours post-dose were omitted. Serum was separated from cells and stored at -20°C until assay. Total serum naproxen was measured by high-pressure liquid chromatography and fluorophotometric detection (Van Loenhout et al., 1982). Serum unbound naproxen measurements were performed after equilibrium dialysis during 5.5 hours at 37°C against phosphate buffered saline.

Pharmacokinetic analysis

The area under the serum drug concentration-time curve AUC(0-12) was estimated according to the linear trapezoidal rule during one dose interval of 12 hours. Total body clearance (CL/F) was calculated as dose (500 mg) divided by AUC(0-12). The elimination half-life of the drug (t1/2) was derived from the line fit by least squares to the last three log concentration-time points: 4, 8 and 12 hours post-dose. An apparent volume of distribution (V/F) was calculated from the product of clearance and half-life divided by 0.693; also, V/F was divided by the body weight to find $V/F.BW^{-1}$. C_0 is the serum naproxen concentration at time 0, immediately before ingestion of the drug; C_{peak} is defined by the individual's highest measured concentration.

Pharmacokinetic parameters concerning protein-unbound naproxen were

calculated as for total naproxen. Naproxen binding affinity to albumin and the number of binding sites was estimated with the aid of a Scatchard plot (Scatchard, 1949). In converting g/l to mmol/l albumin, a molecular weight of 69,000 was used.

Statistical comparisons between groups were made by independent-sample t-testing.

Volunteers gave written and patients verbal informed consent; the study was approved by the University Hospital Ethics Committee.

RESULTS

Total and unbound serum naproxen concentrations of young volunteers and elderly patients are shown in Figure 1; Table II gives the pharmacokinetic data.

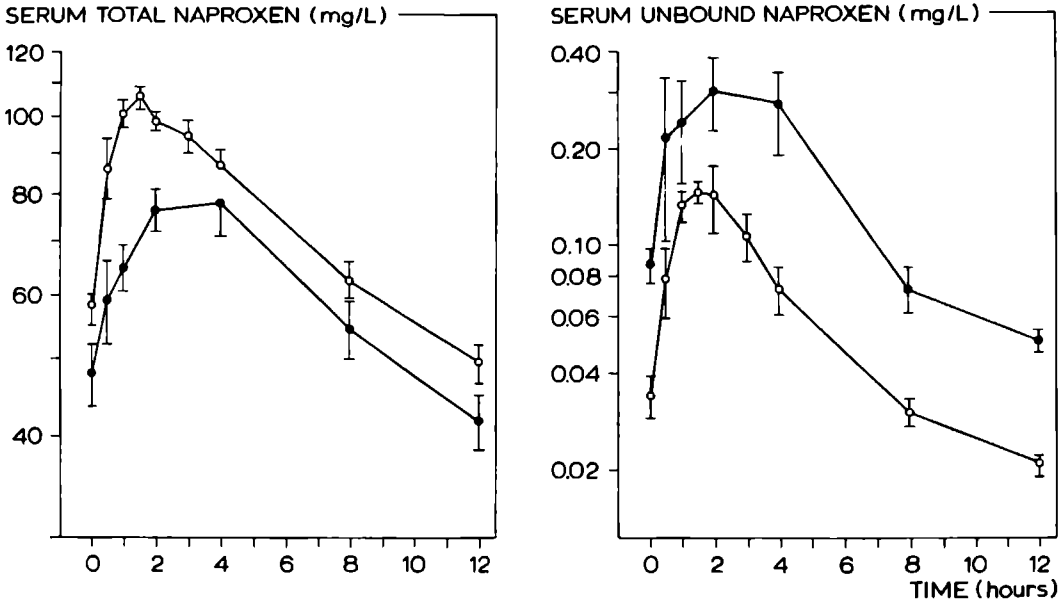

FIGURE 1.
Total (left panel) and unbound (right panel) naproxen serum concentration in 8 healthy young (o) and 6 elderly patients (•) during one dose interval of 500 mg oral naproxen twice daily. Bars indicate the standard error of the mean.

TABLE II. PHARMACOKINETIC DATA (mean ± SD) ON 500 mg ORAL NAPROXEN TWICE DAILY IN YOUNG VOLUNTEERS AND ELDERLY PATIENTS

TOTAL NAPROXEN		YOUNG (n=8)	ELDERLY (n=6)	p
C_0	(mg/l)	57 ± 7	48 ± 11	NS
C_{peak}	(mg/l)	110 ± 7	88 ± 9	<0.001
AUC(0-12)	(mg/l.h^{-1})	896 ± 85	694 ± 139	<0.01
CL/F	(l/h)	0.56 ± 0.05	0.75 ± 0.15	<0.01
V/F	(l)	8.1 ± 1.3	10.4 ± 4.7	NS
V/F•BW^{-1}	(l/kg)	0.11 ± 0.01	0.17 ± 0.06	<0.001
$t_{½}$	(h)	10.0 ± 1.8	9.3 ± 2.3	NS
UNBOUND NAPROXEN				
$(C_0)_u$	(mg/l)	0.03 ± 0.01	0.09 ± 0.02	<0.001
$(C_{peak})_u$	(mg/l)	0.19 ± 0.07	0.41 ± 0.23	<0.05
$AUC(0-12)_u$	(mg/l.h^{-1})	0.74 ± 0.20	1.95 ± 0.60	<0.001
$(CL/F)_u$	(l/h)	713 ± 164	281 ± 96	<0.001
$(V/F)_u$	(l)	5025 ± 1634	1844 ± 1125	<0.01
$(V/F)_u$•BW^{-1}	(l/kg)	72 ± 27	30 ± 16	<0.01
$(t_{½})_u$	(h)	4.8 ± 0.8	4.4 ± 2.0	NS

Statistically significant differences were found for C_{peak}: lower in the elderly, AUC(0-12): smaller in the elderly, CL/F: larger in the elderly, and V/F.BW^{-1}: larger in the elderly. Furthermore, differences were found in protein-unbound naproxen pharmacokinetics: a significantly higher value of the unbound naproxen concentrations $(C_0)_u$ and $(C_{peak})_u$, larger $AUC(0-12)_u$ and smaller $(CL/F)_u$ in elderly patients. $(V/F)_u$ and $(V/F)_u$•BW^{-1} were smaller in the elderly as compared with the young volunteers. Naproxen t1/2 and $(t1/2)_u$ were equal in both groups.

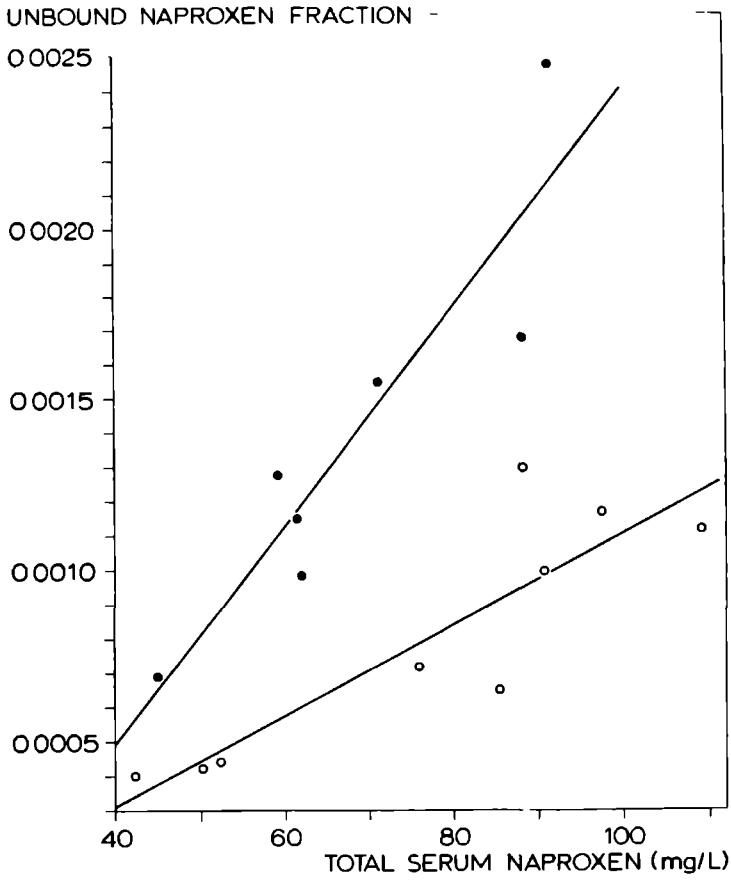

FIGURE 2.
Protein-unbound naproxen fraction versus total serum naproxen concentration in one representative young volunteer (o) and one elderly patient (•). Assuming a linear correlation over the concentration range of total serum naproxen, the equation of the least squares regression line for the young subject is:
$Y = 1.3 \times 10^{-5} X - 2.2 \times 10^{-4}$ with a correlation coefficient r=0.88 and for the elderly subject:
$Y = 3.2 \times 10^{-5} X - 7.9 \times 10^{-4}$, with r=0.92.

The protein-unbound fraction increased with higher total serum naproxen concentrations; in the elderly it was more pronounced than in young healthy volunteers. This is shown in Figure 2 for one representative subject of either group.

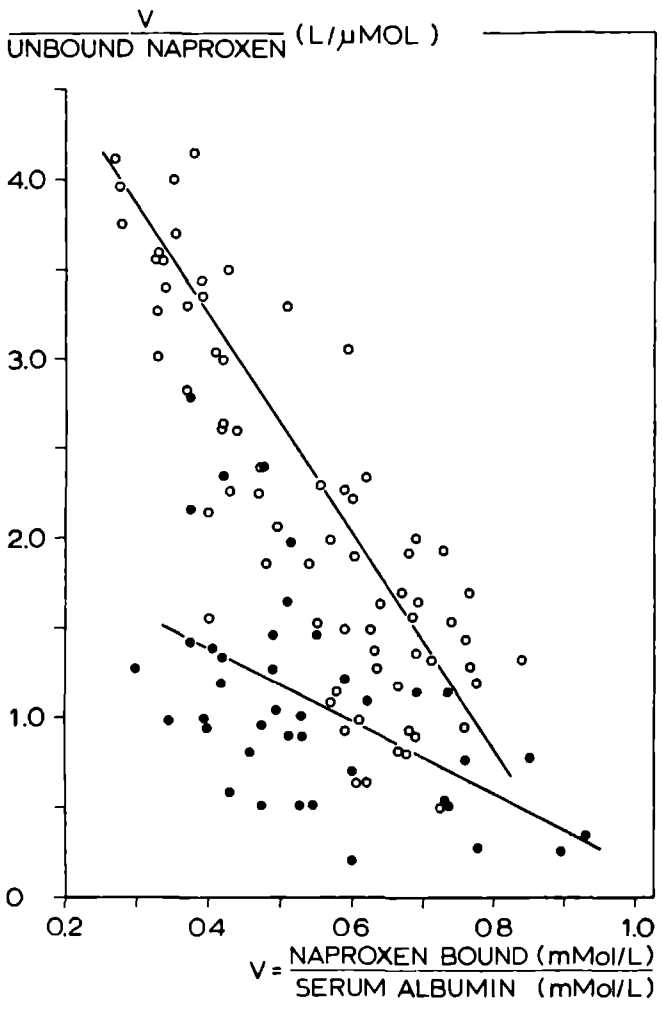

FIGURE 3.
Scatchard plots of naproxen-albumin binding. Open circles (o) represent the data on 8 healthy young volunteers; dots (•) represent the data on 6 elderly patients.

Figure 3 gives the Scatchard plots derived from the data of all serum samples determined in both groups. On the basis of these plots naproxen binding affinity to albumin, as characterized by the association constant (K_a), was significantly lower in elderly

patients ($p<0.001$):

K_a (elderly): 2.0 ± 0.5 l/μmol.

K_a (young) : 5.5 ± 0.4 l/μmol.

The number of binding sites per albumin molecule (n), assuming one single class was:

n (elderly) : 1.1 ± 0.2

n (young) : 0.9 ± 0.2.

DISCUSSION

Naproxen pharmacokinetics in the aged were studied by Upton et al. (1984) in a single and multiple dose study with 375 mg oral naproxen twice daily in young and elderly healthy male volunteers. Mean steady-state plasma concentrations were indistinguishable, but the unbound naproxen fraction was doubled in the elderly males, together with a 50% decrement of the intrinsic clearance. In a recently published study, McVerry et al. (1986) found in geriatric in-patients after a 21-day course of therapy with 500 mg naproxen twice daily a higher mean pre-dose concentration as well as a higher mean pre-dose unbound concentration of the drug, as compared with middle-aged patients. Our study of multiple large doses of naproxen provides further data on altered naproxen pharmacokinetics in aged patients.

The bioavailability of oral naproxen in young volunteers approximates 100% (Runkel et al. 1972). For calculating pharmacokinetic parameters we have assumed an unaltered bioavailability of naproxen in the elderly in view of the completeness of intestinal drug absorption in the aged (Greenblatt et al., 1982). However, we preferred to use the symbol CL/F etc., because one should perform both oral and intravenous studies in the elderly to be certain about naproxen bioavailability. In the patients taking other medication as well, naproxen-drug interaction at the site of absorption was avoided by postponing the intake of co-medication on the day of study. Moreover, the nature of the co-medication makes interference with naproxen protein binding unlikely.

Over 99% of the serum naproxen is bound to albumin; the significant decrease of serum albumin in the elderly patients explains the

lowered C_{peak}, smaller AUC(0-12) and larger $V/F \cdot BW^{-1}$. Serum albumin concentration falls with increasing age (Greenblatt, 1979). Also an inflammatory disease, e.g. an episode of active disease in the course of rheumatoid arthritis, is associated with decreased serum albumin (Baum & Ziff, 1985, Van Den Ouweland, 1986). The two patients with rheumatoid arthritis in our study did not show more pronounced hypoalbuminaemia: 34 and 36 g/l respectively. The mean serum albumin concentration in the elderly was 35 g/l; in our opinion their hypoalbuminaemia was attributable to age. The Scatchard plots indicate that naproxen binding affinity to albumin is significantly smaller in elderly patients. In addition to age-related hypoalbuminaemia it results in an increment in serum unbound naproxen, which is maintained over the dose interval by a decrease of $(CL/F)_u$ to 40% of the value in young volunteers.

In man, conjugation and demethylation of naproxen are the main metabolizing steps before urinary excretion; virtually no unchanged drug is excreted (Upton et al., 1980). We must assume that the moderate impairment in kidney function of elderly subjects cannot explain the reduction in $(CL/F)_u$. The liver represents the major site of drug metabolism. The extremely high values of $(CL/F)_u$ in both elderly and young subjects (281 and 713 l/h respectively) in comparison with estimated hepatic plasma flow, approximately 50 l/h in young adults, suggest that not only the unbound drug but also part of the albumin-bound naproxen is extracted.

In the aged, liver size in absolute terms as well as relative to body weight is diminished and hepatic blood flow is reduced by 40-45%; moreover, complex alterations in biotransformatory pathways have been observed (Greenblatt et al., 1982). Nevertheless phase II reactions in the hepatocyte (drug conjugations) appear to be unaffected by age and the extraction of low clearance drugs is relatively blood flow-independent. The influence of age on hepatic uptake processes in man is unknown. In patients with alcoholic cirrhosis a quantitatively similar loss of unbound naproxen clearance has been shown (Williams et al., 1984); however, the multiplicity of anatomical and metabolic changes due to cirrhosis obviously is not identical with the age-

related alterations in liver histology and function. One can only speculate as to which of the described mechanisms in naproxen elimination is hampered to a certain extent with increasing age and thus causes the loss of $(CL/F)_u$ in elderly patients.

In contrast with the findings of McVerry et al. (1986) we observed a lower mean pre-dose total serum naproxen concentration in the aged patients: 48 ± 11 mg/l in our study as compared with 60 ± 19 mg/l. The lower serum albumin concentration (34±5 g/l) in our patients versus 40.3±3.5 g/l in the study of McVerry readily explains this difference.

It must be noted that for judgeing of naproxen pharmacokinetics in the elderly total drug figures are only partly informative. The lower serum concentrations and even increased CL/F of the total drug are associated with a decreased $(CL/F)_u$ and consequently higher unbound drug concentrations. Naproxen half-life is not significantly changed because of parallel changes in apparent volume of distribution with clearance for both total and unbound naproxen. The differences between t1/2 and $(t1/2)_u$ in each individual ($p<0.01$) must be the result of the concentration-dependent unbound fraction, as shown in Figure 2. $V/F \cdot BW^{-1}$ is largely determined by the intravascular albumin content. The high values of $(V/F)_u \cdot BW^{-1}$ reflect extravascular distribution; the smaller $(V/F)_u \cdot BW^{-1}$ in the elderly possibly results from loss of naproxen tissue binding.

An increase in unbound drug fractions in the aged has been reported for a number of albumin-bound acidic drugs, including NSAID (Wallace & Verbeeck, 1987). This can only partly be explained by a lowered serum albumin concentration. The decrement in naproxen-albumin binding affinity in the aged, as described in this study, is obscure. In most clinical situations the importance of such findings is modest, but if the protein-unbound drug concentration is responsible for desired pharmacological or undesired adverse effects it must be anticipated that the aged patient has an enhanced response to the "normal" dose.

Considering our results and the volunteer data of Upton et al. (1984) it remains advisable to start naproxen treatment in the aged patient

at a low dosage, e.g. 250 mg orally twice daily. When no sufficient therapeutic effect is obtained and this dose has not caused side effects, an increase in dosage is justified.

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CHAPTER IV

NAPROXEN KINETICS AND DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS: A WITHIN-PATIENT STUDY

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(submitted for publication)

LIST OF ABBREVIATIONS

AUC_{0-12}	area under the concentration-time curve during one dose interval
C_0	serum concentration at time 0
C_{peak}	highest measured serum concentration
Cl	clearance
F	bioavailability
ESR	erythrocyte sedimentation rate
k	rate constant
K_a	binding affinity association constant
n	number of independent binding sites
$t1/2\beta$	terminal half-life
u	variables concerning unbound drug measurements
v	ratio of drug bound/albumin
V	apparent volume of distribution

SUMMARY

The effects of rheumatoid arthritis disease activity on pharmacokinetics of the highly albumin-bound non-steroidal anti-inflammatory drug naproxen were studied. Total and protein-unbound serum concentrations were determined in six (male and female) patients with classic rheumatoid arthritis and active polyarticular inflammation during chronic therapy with 500 mg oral naproxen twice daily; the study was repeated at a time when major improvement in disease activity had been achieved.

Naproxen was measured by high-performance liquid chromatography and unbound naproxen concentrations were assayed in buffer after equilibrium dialysis of serum samples.

Active disease in patients with rheumatoid arthritis is commonly associated with hypoalbuminemia: in our patients serum albumin concentration was 30±4 g/l versus 41±2 g/l (mean ± S.D.) at the time-of major improvement. Total naproxen concentrations were significantly lower in the period of active disease, together with a larger apparent volume of distribution (10.6±1.8 l versus 8.4±1.3 l; $p<0.05$) and total body clearance (0.79±1.8 l/h versus 0.59±0.14 l/h;

p<0.001).
Peak unbound naproxen concentrations were 29±19% (p<0.05) lower at the time of improvement (0.40±0.22 mg/l versus 0.26±0.11 mg/l), but unbound trough concentrations (0.06±0.03 mg/l versus 0.06±0.03 mg/l) and unbound concentrations measured after one dose interval up to 60 hours post-dose were similar. The unbound clearance was found diminished during the period of active disease (390±277 l/h) in comparison with improvement (488±343 l/h; p<0.05).
Clinical implications of the pharmacokinetic alterations induced by active polyarticular inflammation in patients with rheumatoid arthritis on chronic naproxen therapy are discussed.

INTRODUCTION

In the management of inflammatory symptoms in rheumatoid arthritis, non-steroidal anti-inflammatory drugs (NSAID) have gained a firm place[1]. Data on pharmacokinetics of the available NSAID generally stem from volunteers; few studies have tried to assess the possible effects of rheumatoid arthritis on drug disposition in patients[2]. Recently we have shown alterations in naproxen kinetics in patients with rheumatoid arthritis during active polyarticular inflammation as compared with healthy young male volunteers[3]. Due to the extensive albumin binding of naproxen, patients had lower serum drug concentrations during the dose interval on chronic intake of 500 mg oral naproxen twice daily, corresponding with their lower serum albumin. In contrast with total drug kinetics, unbound serum concentrations of naproxen were found significantly increased in patients with active rheumatoid arthritis, together with a reduction in clearance and apparent volume of distribution of unbound drug.

Hypoalbuminemia is a common feature associated with exacerbations in disease activity of rheumatoid arthritis, due to an increased catabolism[4] or a combination of catabolism and interleukin-1-dependent reduced albumin synthesis[5]. Apart from the lower serum albumin concentration, other causes of change in naproxen kinetics in patients with rheumatoid arthritis may be: a diminished hepatic drug

TABLE I. DEMOGRAPHIC AND CO-MEDICATION DATA OF 6 PATIENTS WITH RHEUMATOID ARTHRITIS, STUDIED IN A PERIOD OF ACTIVE POLYARTICULAR INFLAMMATION (I) AND IN MAJOR IMPROVEMENT OF DISEASE ACTIVITY (II)

	Gender/age* years	Height cm	Body Weight kg		Smoker		Co-medication**		Time interval between I and II in months
			I	II	I	II	I	II	
A	M/49	179	88	84	+	+	1(150)	1(1500)	11.5
B	F/56	170	77	76	-	+	1(50,2,3,4	1(880),5(2)	8
C	F/59	166	72	73	-	-	1(150),6	1(1500)	8.5
D	F/62	168	58	65	-	-	2,5(10),7	5(5),8	12
E	M/63	175	69	75	-	-	1(2800),9	1(4200)	15.5
F	F/64	173	57	56	-	-	1(150),10	1(200),11(400)	7.5

* age is given as the mean age of I and II

** comedication numericals:
1. aurothioglucose (total cumulative intramuscular dose in mg)
2. acetaminophen 2-3 g/day
3. d-propoxypheneHCL 150 mg at night
4. temazepam 10 mg at night
5. prednisone (daily dose in mg)
6. oxazepam 10 mg at night
7. azathioprine 100 mg/day
8. sulphasalazine 2 g/day, stopped 60 h. before the study until the end
9. cimetidine 600 mg/day, last dose 8 h. before the study, then stopped
10. acenocoumarol stopped 60 h. before the start of the study
11. gold sodium thiomalate (total cumulative intramuscular dose in mg)

metabolism and a modified naproxen albumin binding affinity[6]. We therefore studied naproxen pharmacokinetics in patients with rheumatoid arthritis on two different occasions: first at a time of disease exacerbation and then at a time when remission or at least major improvement in disease activity had been achieved.

PATIENTS & METHODS

Naproxen pharmacokinetics were studied in six patients with rheumatoid arthritis during active polyarticular inflammation (period I), as well as at a time when major improvement of disease activity had been achieved (period II). At the time of period I the patients were hospitalized in the Rheumatology ward, for institution of medical therapy and supportive measures; the study during period II was performed at the patients' residences. Demographic data are listed in Table I. All patients were suffering from seropositive classic rheumatoid arthritis according to the criteria of the American Rheumatism Association[7]. Period II studies were performed at a time when the proposed criteria for a complete remission of rheumatoid arthritis were nearly or completely fulfilled[8].

A complete remission was achieved in patient A, B, E and F; this means that five or more of the following requirements were fulfilled for at least two consecutive months: duration of morning stiffness not exceeding 15 minutes, no fatigue, no joint pain by history, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, ESR < 30 mm/h for a female or < 20 mm/h for a male. Patients C and D had an ESR of 32 and 43 mm/h respectively, and both had three swollen joints; the other criteria were met.

Physical examination before the study revealed no extra-articular manifestations of rheumatoid arthritis and no clinically important other diseases were found. After appropriate investigation the anemia in these patients was diagnosed as anemia of chronic disorders[9]. Hemoglobin concentrations and other laboratory assessments are listed in Table II. The findings of an elevated ESR, elevated C-reactive protein and hypoalbuminemia are consistent with generalized inflammation. There was no significant proteinuria and no

TABLE II. LABORATORY FINDINGS IN THE PATIENTS WITH RHEUMATOID ARTHRITIS DURING ACTIVE DISEASE (I) AND MAJOR IMPROVEMENT IN DISEASE ACTIVITY (II)

	hemoglobin		ESR		C-reactive protein		creatinine		aspartate amino transferase		alkaline phosphatase		γ-glutamyl transpeptidase		albumin	
reference values:	M 8.5-11 F 7.5-10		M <10 F <21		<6		M 60-110 F 50-90		<25		<120		M <40 F <30		37-47	
	mmol/l		mm/h		mg/l		μmol/l		U/l		U/l		U/l		g/l	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
A	8.1	8.5	55	16	23	10	67	67	17	19	90	105	12	13	34	39
B	6.6	8.3	70	15	47	4	75	66	22	17	102	75	20	12	35	44
C	5.3	7.7	113	32	150	6	67	75	14	13	120	143	26	13	25	41
D	5.3	7.6	80	27	132	20	64	56	23	16	86	81	50	20	31	41
E	6.1	8.1	88	5	143	18	99	79	15	13	87	76	18	17	27	40
F	6.2	6.6	77	43	21	26	60	53	20	21	76	93	20	8	29	39

sign of hepatic disease.

Medication

Naproxen was started two to five weeks before the pharmacokinetic study; the patients received 500 mg orally twice daily in tablets of 250 mg Naprosyne^{R} (Sarva Syntex Nederland, Rijswijk, The Netherlands). All except patient D continued naproxen therapy after period I, but at a lower dosage as disease activity diminished. In patient D, naproxen was changed to ibuprofen four months before the study of period II. At least one week before period II all patients were reinstituted on twice daily 500 mg naproxen. On the first day of the study 500 mg naproxen was given orally with breakfast at time 0; the drug was then omitted for the next 60 hours.

Co-medication is listed in Table I; on the first day of the study the morning dose of any medication other than naproxen was postponed until noon. As indicated in Table I, in patient E cimetidine was discontinued 8 hours before study I, in patient F acenocoumarol was discontinued 60 hours before study I and in patient D sulphasalazin was stopped 60 hours before study II until the end of study. During the period of study I, analgesics were administered if needed: patient B and D used acetaminophen and d-propoxypheneHCl. During study II the patients felt no need for analgesics.

Blood sampling and urine collection

Blood samples for total and unbound serum naproxen determinations were taken at time 0, immediately before ingestion of the drug, and after 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48 and 60 hours. After separation of blood cells, serum was stored at -20°C until analysis. At time 0 an indwelling catheter was placed in an antecubital vein. Venous access was kept patent by injection of 50 U heparin sodium solution in 0.5 ml 0.9% NaCl into the rubber capped catheter after each blood sampling. The catheter was removed after 12 hours and further samples were obtained by repeated venipuncture.

At time 0, blood was taken for assessment of ESR, hemoglobin concentration, and serum concentration of C-reactive protein,

alkaline phosphatase, aspartate amino transferase, γ-glutamyl transpeptidase, creatinine and albumin. Laboratory tests were performed according to standard procedures. The freely voided urine was collected at intervals of 12 hours and a sample was stored at -20°C for determination of naproxen and desmethylnaproxen conjugates.

Naproxen determinations

Naproxen in serum and urine samples was assayed by high-performance liquid chromatography and spectrofluorophotometric detection; the coefficient of variation for total serum naproxen (concentration range: 1-125 mg/l) with this method is 1.2%[10]. The unbound serum naproxen concentration in the samples was determined in buffer after equilibrium dialysis at 37°C for 5.5 hours against isotonic Sörensen phosphate buffered saline with pH 7.4. The dialysis cell contained 1 ml serum and 1 ml buffer, separated by a cellulose dialysis membrane (Cuprophane^{R} M150). Adsorption of the drug to the membrane was negligible. The coefficient of variation over the concentration range 0.001-1 mg/l was 4.2%. Storage of samples at -20°C for up to one year did not alter the unbound drug concentrations.

Pharmacokinetic parameters

Bioavailability of 100% was assumed for calculation of pharmacokinetic parameters. Kinetic data on intravenous administration of comparable doses of naproxen to test this assumption are not available, we therefore preferred to use the symbols Cl/F (clearance/bioavailability) and V/F (volume of distribution/bioavailability) throughout the text. Naproxen Cl/F (in l/h), under the assumption of steady state kinetics at time 0, was calculated as: $500/AUC_{0-12}$, where 500 is the dose in mg and AUC_{0-12} is the area under the concentration-time curve during one dose interval of 12 hours in mgh/l. The AUC_{0-12} was estimated using the linear trapezoidal rule. An apparent volume of distribution/bioavailability (V/F, in l) was calculated as: $500/(AUC_{0-12} \cdot k)$, where k is the rate constant (in h^{-1}) obtained from the slope of the log-linear regression line through the last three time points of the dose interval: 4, 8 and 12

hours. The terminal half-life (t1/2β in h) of naproxen was calculated from the slope of the log-linear regression line through the time points 8, 12, 24, 36, 48 and 60 hours post-dose. From the values of unbound serum naproxen concentrations identical calculations were performed to obtain the pharmacokinetic parameters for unbound naproxen.

Albumin binding

Naproxen-albumin binding affinity was studied in a plot according to Scatchard[11]. With the assumption of a single class of binding sites per albumin molecule, the binding affinity constant (K_a) was derived from the slope of the least squares regression line of v/unbound naproxen concentration plotted against v, where v is the ratio of bound naproxen concentration/albumin concentration. To convert the concentration of albumin from g/l to mmol/l, a molecular weight of 69,000 was used. The intercept of the v axis is the number (n) of independent binding sites per albumin molecule.

Statistical analysis

Data obtained in active disease (period I) and in major improvement of rheumatoid arthritis (period II) were analysed for significant differences by the two-tailed t-test for paired samples. Spearman's rank correlation coefficient was used to analyse for a significant relationship between parameters.

Study ethics

The study was approved by the Ethics Committee of the University Hospital St Radboud. Patients gave verbal informed consent.

RESULTS

Together with disease activity-related alterations in hemoglobin, ESR and C-reactive protein, a significant increase in serum albumin concentration was found at the time of improvement in rheumatoid arthritis: 30±4 g/l in period I versus 41±2 g/l in period II; $p < 0.001$. Liver and kidney function tests showed an occasional rise

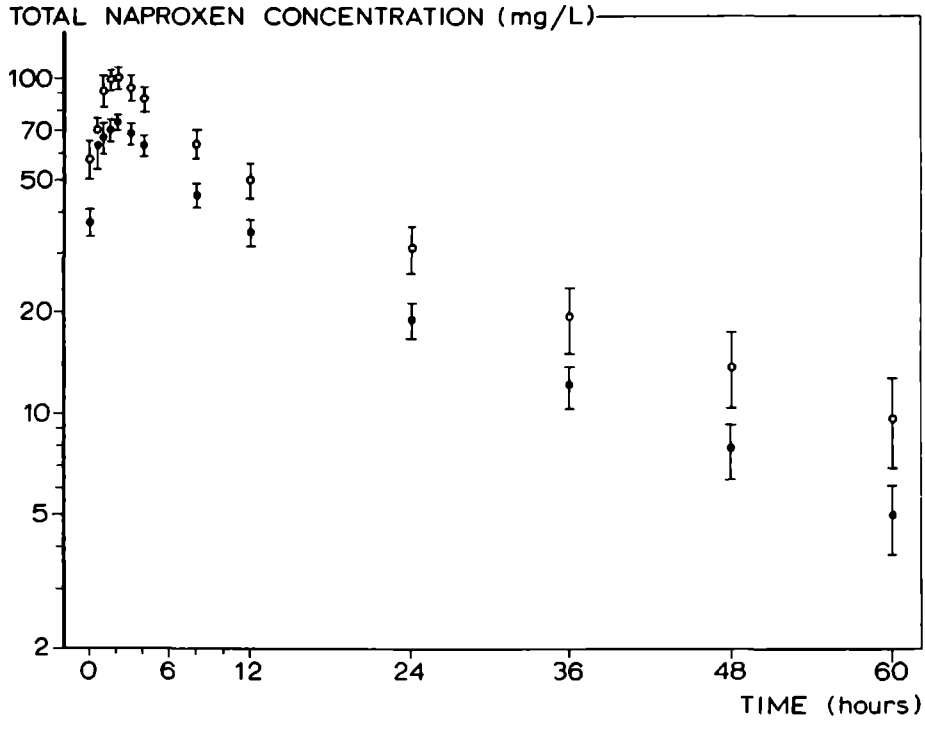

FIGURE 1.
Total serum naproxen concentrations in six patients with rheumatoid arthritis after chronic treatment with 500 mg oral naproxen twice daily. The last dose was administered at time 0. Data are presented at the time of active polyarticular inflammation (●), and at a time when major improvement in disease activity had been achieved (o). Bars indicate standard error of the mean.

or fall without clinical importance. Individual measurements are shown in Table II.

Naproxen serum concentrations over time are graphically depicted in Figure 1 for total and Figure 2 for unbound drug. The points from time 0, the trough drug level at steady state, until 12 hours post-dose represent the naproxen concentrations over one dose interval. Total naproxen concentrations were higher in patients with rheumatoid arthritis at the time of improvement in disease activity: both trough and peak concentrations during the dose interval showed significant

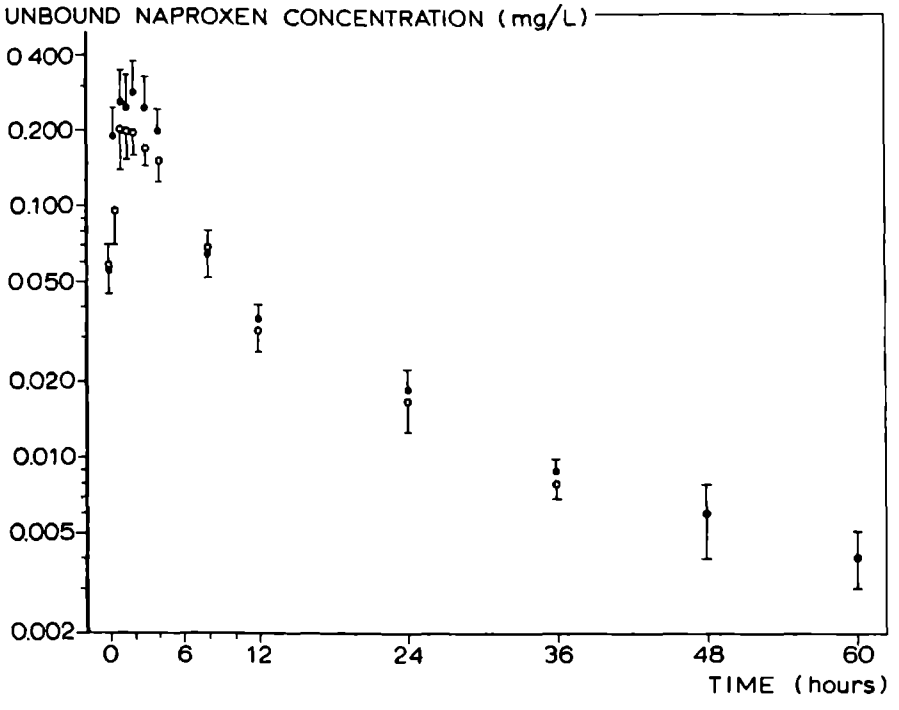

FIGURE 2.
Unbound serum naproxen concentrations in six patients with rheumatoid arthritis in active disease (●), and improvement (o). Bars indicate standard error of the mean.

differences. Pharmacokinetic parameters are listed in Table III. Cl/F and V/F were significantly larger in active disease.

Unbound pharmacokinetics are listed in Table IV. In contrast with total drug kinetics $(Cl/F)_u$ in all patients was found to be larger at the time of improvement in rheumatoid arthritis (390±277 l/h in period I versus 488±343 l/h in period II; $p < 0.05$). Unbound naproxen trough concentrations, as well as the measurements at time points after the dose interval, were indistinguishable in active disease and in improvement. Unbound peak concentrations in all patients were higher in active disease; however, individual differences in mg/l showed a large variability. Mean of period I: 0.40±0.22 mg/l versus 0.26±0.11 mg/l in period II; $0.05 < p < 0.1$). Normalization to

TABLE III. TOTAL SERUM NAPROXEN PHARMACOKINETICS IN PATIENTS WITH RHEUMATOID ARTHRITIS, STUDIED IN ACTIVE POLYARTICULAR INFLAMMATION (I) AND IN MAJOR IMPROVEMENT OF DISEASE ACTIVITY (II)

	C_u mg/l		C_{peak} mg/l		Cl/F l/h		V/F l		$t_{\frac{1}{2}}\beta$ h	
	I	II	I	II	I	II	I	II	I	II
A	27.5	28.0	70.3	80.0	0.99	0.86	11.4	8.5	12.2	12.8
B	25.9	52.2	103.1	104.9	0.79	0.54	9.7	5.8	14.2	15.5
C	39.5	79.5	90.9	125.6	0.72	0.44	12.7	9.0	19.0	27.4
D	44.7	56.2	85.8	113.4	0.69	0.55	8.6	9.3	16.8	20.3
E	43.0	66.0	73.0	99.2	0.82	0.59	9.0	8.4	13.9	14.4
F	43.3	64.4	82.0	107.2	0.73	0.54	12.4	9.4	21.6	21.0
p	< 0.02		< 0.01		< 0.001		< 0.05		N.S.	
mean	37.3	57.7	84.2	105.1	0.79	0.59	10.6	8.4	16.3	18.6
S.D.	8.4	17.3	12.1	15.2	0.11	0.14	1.8	1.3	3.5	5.4

TABLE IV. UNBOUND SERUM NAPROXEN PHARMACOKINETICS

	$(C_u)_u$ mg/l		$(C_{peak})_u$ mg/l		$(Cl/F)_u$ l/h		$(V/F)_u$ l		$(t_{\frac{1}{2}}\beta)_u$ h	
	I	II	I	II	I	II	I	II	I	II
A	0.03	0.01	0.11	0.10	937	1174	9830	7680	10.1	12.8
B	0.03	0.04	0.42	0.22	360	377	1680	1430	16.6	15.1
C	0.09	0.09	0.73	0.32	170	258	868	1291	15.8	15.7
D	0.05	0.05	0.55	0.42	229	296	892	1633	12.9	12.7
E	0.07	0.06	0.28	0.20	299	453	1221	2689	9.8	10.9
F	0.08	0.10	0.32	0.29	344	369	2093	2179	13.5	14.9
p	N.S.		0.05<p<0.1		<0.05		N.S.		N.S.	
mean	0.06	0.06	0.40	0.26	390	488	2764	2817	13.1	13.7
S.D.	0.03	0.03	0.22	0.11	277	343	3494	2438	2.8	1.9

percentage change resulted in a significant mean reduction of C_{peak} from active disease (I) to improvement (II) with 29±19%; $p < 0.02$. (V/F)u and (t1/2β)u showed no significant alterations due to marked individual changes in both directions without an obvious trend.

The individual albumin-naproxen binding affinity constants (K_a) showed a tendency toward increased binding at the time of improvement: see Table V. With the exception of patient F, all K_a values were higher in remission, with a statistically significant increase at a p value < 0.05 in patients C and D. The number of binding sites (n), assuming one class, did not change: n=0.96±0.09 in active disease and n=0.91±0.07 at the time of improvement in rheumatoid arthritis.

TABLE V. NAPROXEN-ALBUMIN BINDING AFFINITY CONSTANTS (K_a in $l \cdot \mu mol^{-1}$), DERIVED FROM SCATCHARD PLOTS IN ACTIVE DISEASE (I) AND IMPROVEMENT (II)

	I		II
A	3.4 ± 0.5		4.2 ± 0.7
B	2.6 ± 0.5		4.6 ± 0.6
C	2.6 ± 0.3	*	5.4 ± 0.4
D	3.8 ± 0.4	*	5.5 ± 0.4
E	4.4 ± 0.8		5.3 ± 0.4
F	6.1 ± 0.5		5.1 ± 0.7

* $p<0.05$

Individual data on the urinary excretion of both naproxen and desmethylnaproxen conjugates during the dose interval (0-12 hours post-dose), as well as the cumulative excretion measured over 60 hours are listed in Table VI. The excretion of naproxen and desmethylnaproxen conjugates was similar in period I and II during one dose interval. The urinary recovery of the total intake of naproxen (500 mg) was 55±6%. The cumulative excretion of naproxen and

TABLE VI. URINARY EXCRETION OF THE TOTAL OF NAPROXEN CONJUGATES AND DESMETHYLNAPROXEN CONJUGATES (in mg naproxen equivalents) AND DESMETHYLNAPROXEN CONJUGATES AS PERCENTAGE OF TOTAL EXCRETION IN ACTIVE DISEASE (I) AND IMPROVEMENT (II)

	excretion during the dose interval				cumulative excretion until 60 hours			
	total conjugates mg		DMNC* %		total conjugates mg		DMNC* %	
	I	II	I	II	I	II	I	II
A	319	341	15	12	498	508	15	14
B	241	251	19	13	372	420	18	15
C	296	289	20	26	445	556	20	25
D	268	257	15	14	504	506	15	15
E	271	279	21	17	432	506	22	18
F	259	240	21	19	474	483	23	22
p	N.S.		N.S.		0.05<p<0. 1		N.S.	
mean	276	276	18	17	454	497	19	18
S.D.	27	36	3	5	49	44	3	4

* DMNC denotes desmethylnaproxen conjugates

desmethylnaproxen conjugates was higher in all patients at the time of improvement; however, inter-individually differences were large. Mean cumulative excretion to 60 hours post-dose in period I was 454±49 mg and in period II it was 497±44 mg; $0.05 < p < 0.1$. Extrapolation to infinity reveals a comparable result: a 12±11% higher cumulative excretion of naproxen equivalents at the time of improvement; $p < 0.05$. The percentage of naproxen equivalents excreted as desmethylnaproxen was similar in period I and II.

DISCUSSION

The importance of clinical pharmacokinetic studies like ours is that they provide the figures of kinetic parameters valid in daily clinical practice. It is therefore inevitable that study entry criteria are not rigid.

Pharmacokinetic studies with naproxen in healthy volunteers showed complete absorption after oral administration of the drug with or without food, in doses up to 4 g[12-14]. Non-linear kinetics, i.e. decreasing increments in AUC upon the intake of subsequent higher dosages have been found, probably due to saturation of naproxen binding[13,15]. After conjugation, the elimination of naproxen and its main metabolite desmethylnaproxen follows the renal route; virtually no unchanged drug is excreted[16].

In our patients with rheumatoid arthritis total and unbound naproxen kinetics evidently show alterations related to activity of the disease: in the period of polyarticular inflammation, lower total serum concentrations are accompanied by a variable but intra-individually always higher peak concentration of unbound drug. The first and most simple explanation for these findings is that hypoalbuminemia in patients with active rheumatoid arthritis leads to saturation of protein binding at a lower total naproxen concentration. Indeed, the percentual increase in serum albumin concentrations as disease activity diminished, was significantly correlated with the percentage increase in the corresponding peak total serum concentrations of naproxen ($r=0.89$; $p < 0.05$). If only saturation of albumin binding would be of importance, one would

expect higher unbound naproxen fractions over the dose interval and no or only short-term elevations in unbound drug concentrations[17]. However, in all patients unbound naproxen concentrations were found elevated at the time of polyarticular inflammation; consequently $(Cl/F)_u$ was diminished in period I as compared with improvement. The similar excretion of naproxen metabolites during the dose interval of both study periods makes fluctuations in bioavailability unlikely. The urinary recovery of 55±6% of the oral dose corresponds with findings in volunteers[3,16].

Factors interfering with naproxen kinetics were avoided where possible, but could not be eliminated with certainty. Drug interactions at the site of absorption were prevented by postponing co-medication. The study was timed so that drugs possibly interfering with naproxen disposition could be discontinued. Nevertheless, co-medication was more extensive in the period of active polyarticular inflammation, than at the time of improvement. Displacing drugs lower the value of K_a[18,19]; moreover in patients with active rheumatoid arthritis, the presence of a modified albumin structure[20] and endogenous inhibitors are other possible origins of lowered K_a values. In vitro protein binding of four different NSAID in serum of ten patients with rheumatoid arthritis was not found different from that in control patients with osteoarthritis[21]. In our study however, significant decrements in naproxen-albumin binding affinity in at least two patients were calculated at the period of active disease. A decrease in K_a allows for higher unbound drug fractions, and only together with a reduction in $(Cl/F)_u$ does this result in higher unbound drug concentrations. Alterations in K_a may be of interest with regard to finding a perfect inverse relationship ($r=-1$) between the differences in K_a in period I and II and corresponding elevations of unbound naproxen peak concentrations.

The consequences of disease activity of rheumatoid arthritis for $(Cl/F)_u$ of naproxen in the patients of this study are obvious. There are no arguments to hypothesize interference of rheumatoid

arthritis disease activity with the renal excretion of conjugated compounds. As shown by the urinary excretion data, the percentage of desmethylnaproxen in total metabolite excretion is similar in periods I and II. Also the total excretion of naproxen metabolites is similar in the dose interval of periods I and II. These findings make alterations in the pathways of metabolism of naproxen less likely, but not impossible. The cumulative excretion of naproxen metabolites to 60 hours post-dose tended to be larger at improvement, but did not reach statistical significance. Also, no significant relationship was found between the increase in urinary naproxen equivalent excretion and the decrease in V/F. As expected, V/F decreased at the time of improvement in disease activity as serum albumin concentrations returned to normal levels.
It appears that the presence of a state of generalized inflammation in the patients with active disease hampers hepatic metabolism of naproxen, and the results of this study suggest that there is a decrease in the rate of hepatic uptake of unbound drug from plasma or in intra-hepatocytic processes.

Hepatic clearance of protein-bound drug is usually described as depending on its extraction ratio (this is the fraction of drug removal in a single pass through the liver). Drug clearance is blood flow-dependent in the case of a high extraction ratio, or dependent on the unbound drug concentration in the case of a low extraction ratio[22]. Naproxen total drug clearance (0.6-0.8 l/h) in relation to an estimate of hepatic plasma flow, 50 l/h in young adults, indicates a low extraction ratio. From the figures of $(Cl/F)_u$: 390 l/h in active disease and 488 l/h in improvement, it follows that the extraction of naproxen in both situations exceeds the unbound drug fraction. Naproxen bound to albumin therefore forms a substantial part of the hepatic uptake. A lower serum albumin serum concentration, as in active polyarticular inflammation of rheumatoid arthritis, might lower the clearance of naproxen; however, the opposite is found: total drug clearance is higher in the presence of hypoalbuminemia.

We conclude that rheumatoid arthritis patients with active polyarticular inflammation have altered naproxen pharmacokinetics, if compared with a period of improvement in disease activity. Together with the lower albumin concentration in active disease a larger V/F and Cl/F is found, without significant change in $t1/2\beta$. Unbound naproxen kinetics show a variable, but significant decrement in $(Cl/F)_u$, consequently higher unbound peak concentrations after ingestion of the drug, but indistinguishable unbound trough concentrations.

Factors possibly explaining the lowered $(Cl/F)_u$ in active disease are diminished hepatic uptake of unbound naproxen from plasma or a hampered metabolism of the drug.

The clinical implications of the findings are:

- a possible beneficial effect of hypoalbuminemia in patients with rheumatoid arthritis and active polyarticular inflammation on the anti-inflammatory effect of naproxen, assuming that unbound drug levels correlate with therapeutic effect;
- the possibility of an increased incidence of adverse drug reactions to naproxen in patients with severe hypoalbuminemia;
- the limited value of total drug concentration measurements as a decision aid for dose adjustments.

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CHAPTER V

HYPOALBUMINAEMIA AND NAPROXEN PHARMACOKINETICS IN A PATIENT WITH RHEUMATOID ARTHRITIS

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Hypoalbuminaemia and Naproxen Pharmacokinetics in a Patient with Rheumatoid Arthritis

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The effects of rheumatoid arthritis (RA) disease activity on non-steroidal anti-inflammatory drug (NSAID) pharmacokinetics have not been extensively studied (Verbeeck et al 1983) Changes in serum albumin concentration together with fluctuations in disease activity could give rise to alterations in the pharmacokinetics of highly albumin-bound drugs In RA patients, serum albumin concentrations are frequently lowered (Baum & Ziff 1985) as a result of increased catabolism (Wikinson et al 1965) During exacerbations of RA an increase in catabolism can explain decrements in serum albumin concentration, paralleling indices of disease activity (Ballantyne et al 1971) This case report describes the changes in naproxen pharmacokinetics during long term administration of naproxen to a patient with RA, as disease activity had diminished and the depressed serum albumin concentration returned to normal

Case Report

Classic RA was diagnosed in a female aged 58 years She had had joint complaints for 1 year and had morning stiffness of 1 hour duration Physical examination revealed symmetrical polyarticular inflammation subcutaneous nodules or other extra-articular manifestations of RA were absent The number of swollen joints was 25, that of tender joints was 4 The Rose-Waaler test was positive at titre 1 : 1024 Other laboratory findings are listed in table I The pathological findings were consistent with the diagnosis of RA In this case there was marked hypoalbuminaemia without clinically significant proteinuria A roentgenogram of the hands showed juxta-articular osteoporosis and narrowing of the interosseous joint spaces and small erosions at several metacarpophalangeal and proximal interphalangeal joints Disease-modifying therapy was started with intramuscular aurothioglucose 50mg per week (Auromyose®, Nourypharma, Oss, The Netherlands) Oral naproxen 500mg was given twice daily in tablets of 250mg (Naprosyne®, Sarva Syntex Nederland, Rijswijk, The Netherlands) Eight months after diagnosis major improvement in disease activity had been achieved At physical examination the patient had 3 swollen joints, no tender joints and no morning stiffness, laboratory findings at time of improvement are given in table I

Methods

Serum samples were taken for determination of naproxen in the third week of treatment and after

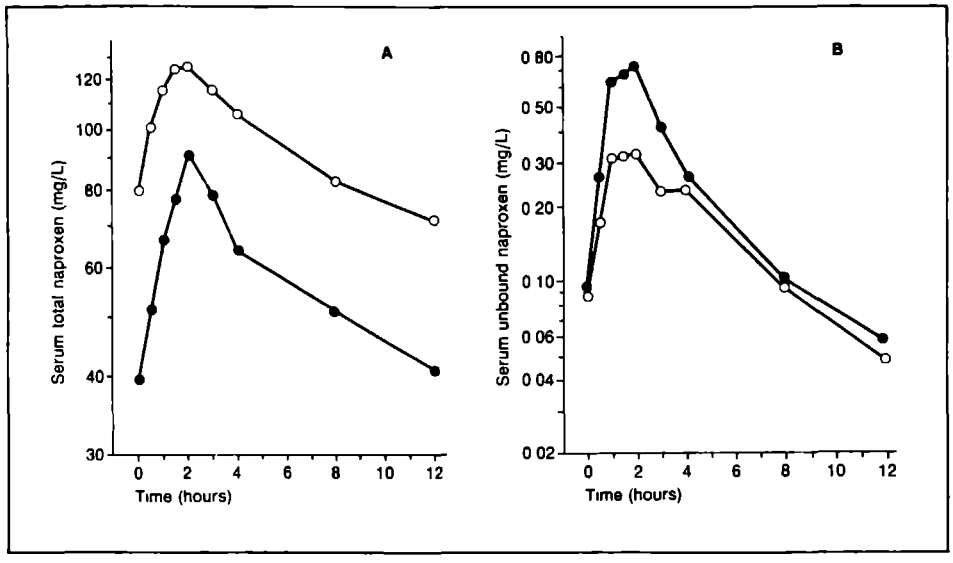

Fig 1. Naproxen concentration-time curves for total (**A**) and unbound (**B**) serum concentrations during long term therapy with 500mg twice daily in a patient with rheumatoid arthritis at the time of active disease (●) and 8 months later when major improvement of disease activity had been achieved (○)

8 months of medication with a total dose of 1.5g aurothioglucose. The first blood sample was drawn immediately before the morning dose of naproxen, the next samples at 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours; the drug was ingested with breakfast. Freely voided urine was collected during this 12-hour period. Serum naproxen and urinary naproxen and desmethylnaproxen conjugates were measured by high pressure liquid chromatography (HPLC) and spectrofluorophotometric detection (Van Loenhout et al. 1982). Unbound naproxen concentrations were determined after equilibrium dialysis during 5 5 hours at 37°C against isotonic phosphate buffered saline with pH 7 4. The dialysis cell contained 1ml serum and 1ml buffer, separated by a cellulose dialysis membrane (Cuprophan® 150M) Complete absorption of the drug after oral intake was assumed for calculation of pharmacokinetics. The area under the concentration-time curve during the 12-hour dose interval ($AUC_{0\text{-}12}$) was esti-

Table 1. Laboratory findings in the patient with rheumatoid arthritis at the time of active disease and 8 months later, when major improvement in disease activity had been achieved with aurothioglucose therapy

	Reference values	Active disease	Improvement
C-reactive protein (mg/L)	< 6 0	150	5 6
ESR (mm/hour)	< 21	113	32
Haemoglobin (g/dl)	12-16	8 5	12 3
Creatinine (μmol/L)	50-90	67	75
AST (IU/L)	< 25	14	13
Total protein (g/L)	60-80	79	71
Albumin (g/L)	37-47	25	41
Urinary protein (g/24h)	< 0 10	0 16	0 15
Bodyweight (kg)		72 4	73 0

Abbreviations ESR = erythrocyte sedimentation rate, AST = aspartate amino transferase (SGOT)

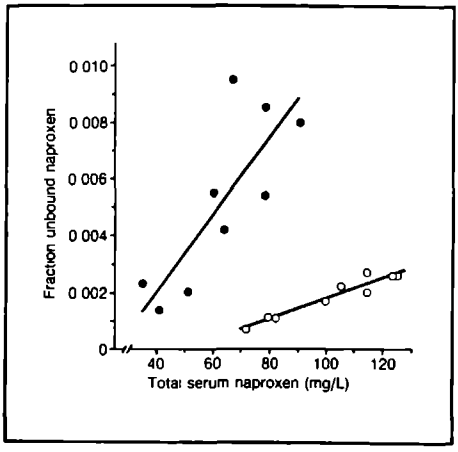

Fig 2 Fraction of unbound naproxen (f_u) *versus* the total serum naproxen concentrations in a patient with rheumatoid arthritis at the time of active disease (●) and improvement (○) The f_u on both occasions shows concentration dependency

mated according to the linear trapezoidal rule Total body clearance (CL) was calculated as dose/ $AUC_{0\text{-}12}$ The elimination rate constant (k_{el}) to describe the 12-hour interval was obtained from the slope of the log-linear regression line through the last 3 concentration-time points (i e 4, 8 and 12 hours post-dose) [elimination half-life, $t_{1/2\beta} = k_{el}^{-1} \cdot 0\,693$]

The volume of distribution (Vd) was calculated from CL/k_{el} From the values of unbound serum naproxen concentrations identical calculations were performed to obtain the unbound naproxen pharmacokinetics $AUC_{0\text{-}12u}$, CL_u, Vd_u and $t_{1/2\beta u}$

Results

The concentration-time curves for total and unbound naproxen are shown in figures 1A and 1B, respectively, pharmacokinetic parameters are presented in table II At the time of improvement the serum concentrations of total naproxen were much higher than those in the phase of active disease, with only minor differences in $t_{1/2\beta}$, with the unbound naproxen concentration only the peak values were different those in the phase of active disease being the highest Data on urinary excretion of naproxen metabolites are given in table III The recovery of drug metabolites in the urine on the 2 occasions was similar

The naproxen fraction unbound (f_u), both during the phase of active disease and major improvement, showed serum drug concentration dependency, the f_u observed in each serum sample, as well as the least-square lines through the points of the respective concentration interval, are shown in figure 2 Correlation coefficients were $r = 0\,80$ ($p < 0\,01$) for active disease and $r = 0\,96$ ($p < 0\,001$) for the time of major improvement, with the assumption of a linear correlation over the range of concentrations

Discussion

The pharmacological properties and therapeutic applications of naproxen [(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid] have been reviewed by

Table II Naproxen pharmacokinetics in the described patient during long term therapy with 500mg twice daily Data at the time of active disease compared with those at the time of improvement

	Active disease	Improvement
C (time 0) [mg/L]	39 5	79 5
C_u (time 0) [mg/L]	0 09	0 09
C peak (mg/L)	90 9	125 6
C_u peak (mg/L)	0 73	0 32
$AUC_{0\text{-}12}$ (mg/L · h)	699	1134
$AUC_{0\text{-}12u}$ (mg/L · h)	2 94	1 94
CL (L/h)	0 72	0 44
CL_u (L/h)	170	257
Vd (L)	12 7	9 0
Vd_u (L)	869	1291
$t_{1/2\beta}$ (h)	12 3	14 1
$t_{1/2\beta u}$ (h)	3 5	3 5

Abbreviations C = serum concentration C = serum concentration of unbound drug AUC = area under concentration time curve CL = clearance Vd = volume of distribution $t_{1/2\beta}$ = elimination half life

Table III Urinary excretion (mmol/12h) of naproxen and desmethylnaproxen conjugates active disease compared with improvement

	Active disease	Improvement
Naproxen conjugates	1 03	0 93
Desmethylnaproxen conjugates	0 25	0 33
Total excretion of naproxen equivalents (mg/12h)	1 28 (296)	1 26 (289)

Brogden et al (1975) Naproxen is highly albumin bound, with an f_u varying between 0 001 and 0 01 in the patient described in this report From volunteer studies by Runkel et al (1976) it is known that naproxen administered in stepwise increased doses is subject to increasing metabolism due to its concentration-dependent f_u, leading to lower-than-expected rises in $AUC_{0-\infty}$ At the time of active disease a higher unbound naproxen peak concentration was found in our patient, and an increased CL resulted in a smaller AUC The serum albumin concentration in the patient rose markedly, from 25 g/L at the time of active disease to 41 g/L when major improvement in RA had been achieved We thus expected to find an alteration in naproxen pharmacokinetics more pronounced than in other patients with a comparable disease history but less striking changes in the serum albumin concentration It is possible that RA disease activity affects not only the serum albumin concentration but also the albumin ligand binding *per se* From the observations in this case binding characteristics (assuming a single class of binding sites) were calculated (Scatchard 1949)

At the time of active disease

$K_a = 2\,5 \pm 0\,4$ L/μmol
(95%CI 1 5-3 5 L/μmol)
$n = 1\,0 \pm 0\,2$ (95%CI 0 5-1 6)

At the time of improvement

$K_a = 5\,4 \pm 0\,4$ L/μmol
(95%CI 4 6-6 2 L/μmol)
$n = 0\,9 \pm 0\,2$ (95%CI 0 6-1 3)

where K_a = association constant, n = number of binding sites, figures are given as mean ± SD (95% Confidence Interval)

Evidently these association constants are different This raises the question whether administration or endogenous compounds had displaced naproxen from the albumin At the time of active disease the patient was hospitalised and all drug intake was monitored she did not use aspirin or any other NSAID Aurothioglucose is not known to be a drug displacer of clinical importance Serum concentrations of gold during aurothioglucose therapy are comparable with those reached with aurothiomalate 1 to 4 mg/L (Gottlieb et al 1974, Van Riel et al 1983) After 40 weeks of aurothioglucose therapy, Van Riel and colleagues (from this institute) found a mean serum gold concentration of 1 5 ± 0 7 mg/L in 10 patients with RA – less than 5% of the naproxen concentration on a molar base Endogenous compounds able to displace drugs from serum proteins in a way comparable to the situation in renal failure (Reidenberg & Drayer 1984), have not been reported in serum of patients with active RA The literature concerning modulation of NSAID-protein binding in RA patients is scanty and presents conflicting results (Selley et al 1978, Wanwimolruk et al 1982) Literature on alterations in naproxen pharmacokinetics following long term administration is not available In this case, except for RA disease activity, no variables affecting drug kinetics appeared to have changed

The relative increments of both Vd and CL in active disease compared with improvement were nearly equal, therefore, $t_{1/2\beta}$ was less affected Differences between $t_{1/2\beta}$ and $t_{1/2\beta u}$ can be explained by the alterations of f_u over the naproxen concentration range The values of CL_u, given in table II, were remarkably high in active disease as well as in improvement and exceeded the plasma flow through the liver and kidneys together This must be due to the fact that naproxen albumin binding is not the absolute limiting factor in the drug's metabolism during the passage of albumin-bound drug through the liver part of the bound fraction is also metabolised We are unable, at present, to provide an interpretation of the differences we found be-

tween CL_u in active disease and that in improvement; it is possible that exacerbations in RA affect the capacity of the liver to metabolise naproxen.

The amount of naproxen, and metabolite conjugates recovered in the urine during the dose interval (59 and 58% of the ingested dose, respectively) corresponds well with data from volunteers given naproxen 500mg twice daily: 57 ± 10% (Upton et al. 1980). In this case, therefore, the bioavailability of naproxen both in active disease and in improvement must have been the same, and it may be hypothesised that absorption was nearly complete. The unchanged excretion of desmethylnaproxen indicates the unaltered pathways of the drug's metabolism. These arguments support the view that changes in serum albumin cause the pharmacokinetic differences described.

Therapeutic Implications

The implications of the high unbound concentrations of naproxen, as in this patient with active RA, are not yet clear. Data on the possible relationship between the occurrence of side effects and high unbound naproxen concentrations are not available. To date, the incidence of side effects during treatment of patients with active RA has not been found to be increased, even at naproxen doses up to 1.5g daily (Day et al. 1982). The higher unbound drug concentrations, especially in patients with more active disease, may even be favourable if the anti-inflammatory effects of naproxen correlate with its unbound serum concentration. It has to be concluded that, in the case presented, the effects of RA disease activity on the pharmacokinetics of naproxen were impressive. Together with a major improvement in the RA, the subject's serum albumin concentration rose from 25 to 41 g/L, resulting in a 30 to 40% decrease in Vd and CL; the peak unbound naproxen concentration in improvement was only half its level in the active disease state.

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CHAPTER VI

GASTROINTESTINAL BLOOD LOSS DURING TREATMENT WITH NAPROXEN FOR TREATMENT OF RHEUMATOID ARTHRITIS

FA van den Ouweland, FHM Corstens,
LBA van de Putte and FWJ Gribnau

Scand J Rheumatol (accepted for publication)

ABSTRACT

In 9 patients with active rheumatoid arthritis we studied gastrointestinal blood loss during well tolerated therapy with the non-steroidal anti-inflammatory drug naproxen 500 mg twice daily. The mean gastrointestinal blood loss, assessed with reinfused autologous ^{51}Cr-labelled erythrocytes, was 1.4 $\pm$ 0.6 ml/day (mean $\pm$ SD) and did not exceed the upper normal level. No relationship was observed between individual gastrointestinal blood loss and serum concentrations of protein-unbound or total naproxen, or the duration of drug treatment, or the degree of disease activity of rheumatoid arthritis. Two subjects developed peptic ulcer disease after the study, in which they had a blood loss of 0.9 and 1.9 ml/day, respectively.

INTRODUCTION

Adverse drug reactions, originating from the gastrointestinal tract, constitute the major part of problems with non-steroidal anti-inflammatory drug (NSAID) therapy for joint diseases. The different NSAIDs have an inhibition of prostaglandin synthesis in common, and gastrointestinal mucosal lesions seem to be inevitably linked with this pharmacological action. We studied naproxen, a highly albumin-bound NSAID, frequently used for the symptomatic treatment of rheumatoid arthritis. Protein-unbound serum naproxen concentrations were found elevated, due to disease-associated hypoalbuminaemia in patients with rheumatoid arthritis and active polyarticular inflammation, either in comparison with healthy young volunteers (1) or within the same patient at a moment that major improvement in disease activity had been achieved (2). It can be hypothesized that gastrointestinal damage is related with the protein-unbound drug concentration, so the observation of higher unbound drug concentrations in patients with active rheumatoid joint inflammation prompted us to study the possibility of increased gastrointestinal lesions in that phase of disease during naproxen therapy. Therefore we measured gastrointestinal blood loss, using the method of reinfused ^{51}Cr-labelled erythrocytes.

PATIENTS AND METHODS

Subsequent patients with classic or definite rheumatoid arthritis according to the criteria of the American Rheumatism Association (3), hospitalized in view of active disease, were invited to enter the study if naproxen therapy was continued or was initiated on admission by the caring physician. Nine patients, 5 women and 4 men, aged 54±8 years (mean ± SD) entered the study. The clinical and laboratory findings in these patients are presented in Table I. For each patient an index of disease activity (4) was assessed; it was calculated by grading on a 4-point scale the haemoglobin concentration, the erythrocyte sedimentation rate according to the Westergren method, the number of tender joints and the duration of morning stiffness; the total was then divided by four. In all patients the anaemia was diagnosed as anaemia of chronic disorders (5). None had abdominal discomfort or ulcer complaints from the start of naproxen treatment until the end of the study. Two female patients had a history of ulcer disease. All patients received disease modifying drug treatment: 50 mg intramuscular aurothioglucose weekly (n=3), 100 mg oral azathioprine daily (n=2), 100 mg oral azathioprine plus prednisone 5, 7.5 and 10 mg daily respectively (n=3), 500 mg oral d-penicillamine daily (n=1). All patients used oral naproxen at a dosage of 500 mg twice daily at least 5 days before ^{51}Cr labelling of erythrocytes.

^{51}Cr labelling of autologous erythrocytes was performed using standard Nuclear Medicine techniques (6). Venous blood was drawn and collected in ACD-A anticoagulant. After removal of plasma, 50 μCi 1.85 MBq) $Na_2{}^{51}CrO_4$ in 0.9% NaCl was added; the mixture was incubated at 37° C for 15 minutes. The labelled red cells were washed twice in 0.9% NaCl before intravenous reinfusion. On each of the next 7 days a venous blood sample was drawn to determine ^{51}Cr radioactivity. From the moment of reinfusion on, the total amount of stools was collected. On the 7th day after reinfusion 2 g oral carmine was administered and stool collection continued until the first appearance of red-coloured faeces to correct for individual bowel transit time. After completion of the stool collection the

TABLE I. CLINICAL AND LABORATORY DATA IN NINE PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS (RA)

Patient/ sex/age	Duration of RA	Duration of naproxen use	Concomitant medication*	Hgb	ESR	Morning stiffness	Number of tender joints	IDA
	years	days		mmol/l	mm/h	hours		points
1/F/52	15	28	3	6.9	42	2	6	2.25
2/M/49	0.3	22	1	8.1	55	1	10	2.75
3/F/41	19	12	2,4	6.3	72	4	24	3.5
4/F/56	0.2	49	1	6.6	70	1.5	19	3.25
5/M/60	7	40	2	7.7	22	0.5	25	2.75
6/F/65	0.2	17	2	6.2	65	2	5	2.75
7/F/61	1	13	2,4	5.3	81	2.5	30	3.75
8/M/59	0.2	21	1	5.8	7	2	4	2.5
9/M/47	14	16	2,4	7.1	67	0	4	2.25

*Concomitant medication: 1 = aurothioglucose; 2 = azathioprine; 3 = d-pencillamine; 4 = prednisone.

Hgb = haemoglobin concentration, reference values: F: 7.5-10.0 ; M: 8.5-11.0 mmol/l

ESR = erythrocyte sedimentation rate, reference values: F: < 21; M: < 10 mm/h

IDA = index of disease activity.

faecal ^{51}Cr radioactivity was counted in a geometrically independent whole body counter. The mean gastrointestinal loss of blood in ml/day was calculated from the mean faecal radioactivity excreted per day, divided by the mean blood radioactivity per ml. The total body radiation dose from the infused ^{51}Cr was estimated as approximately 0.74 mrem/μCi (0.21mSv/MBq) (7).

Total and unbound naproxen concentrations were determined during one dose interval of 12 hours. Serum samples were taken at time 0 and at 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours after the morning dose of the drug. Naproxen was measured with HPLC and spectrofluoriphotometric detection (8). The unbound drug concentration was determined after equilibrium dialysis. The peak concentration (C_{peak}) was the highest concentration observed; the average concentration (C_{av}) was calculated from the area under the concentration-time curve, estimated with regard to the linear trapezoidal rule.

STATISTICAL ANALYSIS

Spearman's rank correlation was used to analyse for significant relationship between parameters.

STUDY ETHICS

The study was approved by the Ethics Committee of the University Hospital St Radboud and was performed in accordance with the principles laid down in the Declaration of Helsinki. Patients had given verbal informed consent.

RESULTS

In all subjects a complete stool collection allowed measurement of the gastrointestinal blood loss over a 7-day period. The mean daily faecal blood loss of the 9 patients with active rheumatoid arthritis was: 1.4 ± 0.6 ml (mean ± SD). The median of the daily blood loss was 1.1 ml. The individual mean daily gastrointestinal blood loss was not correlated with either the C_{peak} or with the C_{av} of serum unbound and total naproxen; Table II gives the individual data.

TABLE II. GASTROINTESTINAL BLOOD LOSS AND PROTEIN-UNBOUND AND TOTAL DRUG CONCENTRATIONS IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS DURING TREATMENT WITH 500 mg ORAL NAPROXEN TWICE DAILY

Patients	Mean blood loss ml/day	C_{peak} unbound µg/l	C_{av} unbound µg/l	C_{peak} total mg/l	C_{av} total mg/l
1	0.6	202	77	110	74
2	0.8	109	45	70	42
3	0.9	126	70	85	66
4	0.9	415	80	103	51
5	1.1	175	74	83	55
6	1.9	403	151	83	58
7	2.0	547	182	86	61
8	2.1	129	60	91	62
9	2.1	206	74	90	49

The individual mean daily gastrointestinal blood loss obviously showed no relationship with the duration of exposure to the naproxen regimen of 1 g daily before ^{51}Cr labelling of red cells was performed, nor with the interval between the diagnosis of rheumatoid arthritis and the performance of this study. Furthermore, no relationship was found between the mean daily faecal blood loss and the assessed index of disease activity. Individual results are presented in the Figure.

DISCUSSION

Since the well-documented study of Stubbé (9) it has been known that, during treatment of rheumatoid arthritis with acetyl-salicylic acid, faecal blood loss is detectable with the benzidine reaction in 70% of the patients; in that study a positive benzidine reaction corresponded with a daily loss of 4 ml blood or more. Later Leonards

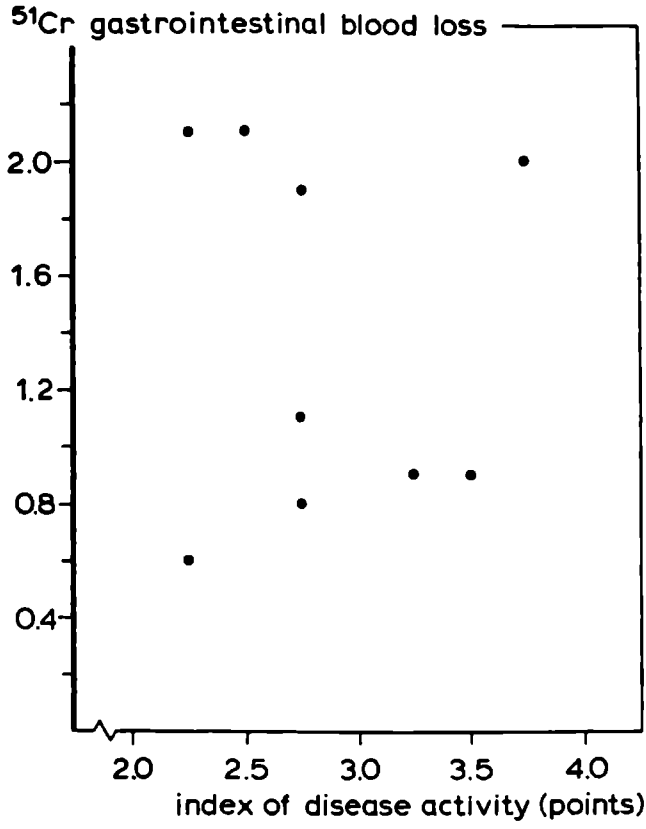

FIGURE.
Mean daily gastrointestinal blood loss determined after reinfusion of ^{51}Cr-labelled erythrocytes in 9 patients with active rheumatoid arthritis, during treatment with 500 mg oral naproxen twice daily, plotted against the index of disease activity.

et al. (10) observed in volunteers, given aspirin 3.6-4.5 g daily over a 28 day period a mean gastrointestinal blood loss, measured with autologous ^{51}Cr-labelled erythrocytes, of 3.6 ± 2.2 ml/day. Naproxen, in comparison with aspirin has been reported to cause a significantly smaller gastrointestinal blood loss in rheumatoid arthritis patients (11). With regard to the results of previous ^{51}Cr-labelled red cell studies with volunteers and out-patients during naproxen administration, listed in Table III, the amount of gastrointestinal blood loss in our study is in the same order of magnitude. We compared our findings with data from literature,

TABLE III. DATA ON GASTROINTESTINAL BLOOD LOSS, MEASURED WITH ^{51}Cr-LABELLED ERYTRHOCYTES FROM PATIENT AND VOLUNTEER STUDIES

Reference	Number of subjects	Patients/ Volunteers	Daily naproxen dosage (mg)	Gastro-intestinal blood loss* (Mean±S.D.)
Lussier et al. (12)	6	V	500	1.5 ± 0.6
Magnusson et al. (13)	12	V	500	2.0 ± 1.9
Lussier et al. (11)	6	P	750	1.0 ± 0.5
Salom et al. (14)	9	V	750	1.2 ± ?
This study	9	P	1000	1.4 ± 0.6

*Results are presented in ml/day, except for reference 11, where gastrointestinal blood loss is given in ml/sample of faeces.

because it was judged unethical to withdraw NSAID treatment from our patients with active polyarticular inflammation for a sufficiently long period to make an assessment of the individual baseline faecal excretion of ^{51}Cr radioactivity. Both the mean (1.4 ml/day) and the median (1.1 ml/day) gastrointestinal blood loss in our 9 patients with active rheumatoid arthritis is below the upper normal level of faecal excretion of ^{51}Cr-labelled, reinfused autologous erythrocytes: 1.5 ml/day (mean + 2 x SD from 148 subjects) (15).

In man, the presence of rheumatoid arthritis per se has never been shown to aggravate NSAID-induced gastrointestinal mucosal lesions; this in contrast with polyarthritic animals showing more gastric bleeding than controls (16). The gastroscopic finding of more mucosal lesions during a one week regimen of 750 mg naproxen daily, in comparison with 500 mg daily in the preceding week (17), suggests the existence of a dose- or concentration-effect relationship for gastrointestinal damage. A volunteer study of ^{51}Cr faecal blood loss during long-term administration of 20 mg piroxicam daily, showed an

increase in gastrointestinal blood loss with time, until after the second week of piroxicam administration a steady state serum level was achieved (18). This points to either a certain period of time needed to produce ^{51}Cr loss by mucosal lesions, or a concentration-effect relationship. In our study, all patients started to use naproxen at least five days before the study; so sufficient time to reach stable pre-dose concentrations had elapsed. For a highly protein-bound drug (naproxen albumin binding exceeds 99%) the unbound serum concentration is a more meaningful value to study drug pharmaco-dynamics; both the peak and average serum concentrations of unbound naproxen were therefore analysed for a possible correlation with the individual gastrointestinal blood loss of the patients. Taking together the results of this and of the previous studies (11-14), the amount of gastrointestinal blood loss, measured with ^{51}Cr red cells, fails to show an evident dose or concentration dependency during treatment of volunteers and rheumatoid arthritis patients with naproxen in the dose range 0.5-1 g daily.

In two women (patients 3 and 6) peptic ulcer disease developed one and four weeks after finishing the study. Both had a history of peptic ulcer disease in the past: in patient 3 in association with the use of indomethacin and in patient 6 unrelated with NSAID therapy. Patient 3 presented with complaints of typical abdominal pain on the 20th day of naproxen administration; endoscopic examination revealed a small superficial pyloric ulcer and multiple mucosal lesions in the duodenal bulb. Patient 6 presented at the 50th day of naproxen administration with sudden appearance of tar-coloured stools preceded by vague complaints of a short duration; endoscopy showed a bleeding gastric ulcer at the lesser curvature. Anaemia had worsened from a haemoglobin concentration of 6.2 to 4.1 mmol/l.

We conclude that, although the number of observations is limited, that patients suffering from the most active rheumatoid arthritis did not show the largest gastrointestinal blood loss. In the majority of the patients with active rheumatoid arthritis the blood loss was well below the upper normal level; the amount of gastrointestinal blood loss in the patients was not related to the duration of naproxen

treatment. Therefore, if pathological faecal blood loss is observed in patients with active rheumatoid arthritis during naproxen therapy, this is most likely due to other, individual causes and merits careful diagnostic investigation; clinical data support this view (19). Finally, individual patients evidently develop peptic ulcer disease without a preceding gastrointestinal blood loss of major clinical importance. The absence of a more than expected ^{51}Cr loss has no predictive value for ulcerogenesis.

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CHAPTER VII

CONGESTIVE HEART FAILURE DUE TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN THE ELDERLY

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Age Ageing (accepted for publication)

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AS A PROGNOSTIC FACTOR IN ACUTE PULMONARY EDEMA

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(with permission of the editor)

SUMMARY

Congestive heart failure possibly due to treatment with non-steroidal anti-inflammatory drugs in the elderly was studied by means of a questionnaire to the participants of a postgraduate course on locomotor diseases in the elderly, and by analysis of the hospital records of 600 elderly subjects diagnosed with congestive heart failure. The questionnaire revealed 22 possible cases, reported by 20 physicians (84 physicians out of 243 responded the questionnaire).

In the hospital population 5 probable cases were detected. Details of these patients are presented. In contrast with findings in literature, in no case was solute retention the result of kidney function impairment.

The specific problems regarding the attributability of this adverse effect are discussed. The results of our study give further evidence that congestive heart failure due to non-steroidal anti-inflammatory drug treatment is a probable adverse drug reaction in elderly individuals with or without a history of impaired cardiac performance. It may result from drug toxicity following (relative) overdosing in this age group, from reduced effectiveness of concomitant diuretic treatment or from effects on cardiovascular homoeostasis.

INTRODUCTION

The incidence of locomotor diseases increases throughout life and so does drug use for its treatment[1]. The occurrence of water and salt retention, as well as resistance to diuretics, has been reported as a side effect of non-steroidal anti-inflammatory drugs (NSAID)[2-5] and occasionally this may result in congestive heart failure (CHF)[6]. To assess CHF as a side effect of NSAID therapy in the elderly, we asked general practitioners and nursing home physicians whether they had noticed possible cases and we also performed a retrospective study in the patient population of the University Hospital St Radboud.

METHODS

Study part I: we sent a questionnaire to the participants of a local postgraduate course on locomotor diseases in the elderly to collect their cases suggesting CHF during NSAID treatment. We asked the participants whether such a case had ever been noticed by them and, if so, to provide details about this patient on a structured answer form. If respondents reported never to have seen this side effect, we asked to indicate this; we also asked whether they were familiar with the possibility of CHF induced by NSAID. The subject had been mentioned, but not with particular emphasis, during the preceding course; the mailing of the questionnaire had not been announced.

Study part II: in retrospect the medical records of 600 patients from the Department of Internal Medicine and Cardiology, diagnosed as CHF within the five-year period 1981-1985, were screened for concomitant locomotor diseases, being the main indication for NSAID prescription. Diagnoses in this hospital are classified according to the 9th Clinical Modification of the International Classification of Diseases[7] (ICD-9-CM). CHF had been diagnosed if at least one episode of left or right ventricular failure[8] had occurred; concomitant locomotor disease comprised the diagnoses 710-739 and diagnosis 274 according to ICD-9-CM. Kidney function was assessed with the aid of a nomogram using serum creatinine, body weight, age and gender as variables[9].

RESULTS

Physicians' questionnaire (Study part I): 243 forms were mailed three weeks after the postgraduate course; 84 (35%) were returned. The 84 respondents are listed according to their professional status in Table 1. Of the respondents, 20 reported having observed one or more patients with CHF after starting NSAID therapy, resulting in a total number of 22. In 5 patients the event took place less than one month, and in four between one and eight months before the questionnaire was mailed; another 13 patients were reported with CHF occurring more than one year before this study. Of the responding physicians not reporting a case, 48% were familiar with CHF as an adverse effect of NSAID therapy.

TABLE I. PROFESSIONAL STATUS OF PHYSICIANS RECEIVING THE QUESTIONNAIRE ON CHF DUE TO NSAID THERAPY AND OF THE RESPONDENTS

Professional status of the physicians	participating physicians n (%)	responding physicians n	physicians observing CHF n
general practitioners	150 (62)	46	11
nursing home physicians	64 (26)	32	8
internists	11 (4.5)	4	1
geriatricians	7 (3)	1	0
physicians in training	11 (4.5)	1	0

Twenty-two patients were reported, but only 13 cases could be documented in detail (Table II). These 13 patients were aged 81±9 years (mean±SD); there were 11 females and 2 males; 9 of the 13 definitely had suffered from heart failure at least once before. The other four patients were not known with this diagnosis to their physician; however, all four used diuretic therapy. The time interval between the start of NSAID treatment and the diagnosis of CHF in the 13 cases ranged from 2 days to several years, but the median time interval was one month.

Patient record analysis (Study part II): the medical records of 600 patients with CHF were screened for the existence of concomitant locomotor diseases. Of the 58 patients with such a combination of diagnoses, 22 had been treated with a NSAID at the time of heart failure. The indications to prescribe a NSAID were: osteoarthritis (n=10), rheumatoid arthritis (n=9), polymyalgia rheumatica (n=1), gouty arthritis (n=1) and hypertrophic osteoarthropathy (n=1). The 22 patients had a mean age of 77±5 years, there were 16 females and 6 males. The mean creatinine clearance at the time of CHF was: 56±19 ml/min. Apart from CHF, other clinically important diagnoses in these 22 patients were: atrial rhythm disturbances (atrial

fibrillation, flutter and sick sinus syndrome) (n=13), myocardial infarction in the history (n=9), angina pectoris (n=9), diabetes mellitus (n=7), hypertension (n=6), chronic obstructive lung disease (n=4), peptic ulcer disease in the history (n=3), valvular heart disease (n=2), bronchial carcinoma (n=1).

In the group of 22 CHF patients, 7 used NSAID chronically and for 2 patients the duration of therapy had not been recorded. The median time interval between CHF and the start of NSAID treatment was 2 months.

In 17 of 22 cases a probable cause, not primarily NSAID related, to explain the occurrence of CHF was determined: onset of atrial fibrillation or flutter (n=7), echocardiographically confirmed congestive cardiomyopathy existed in 3 of these cases; cessation of diuretics or failure to comply with the medication (n=5) or with dietary salt restriction (n=4); myocardial infarction complicated by CHF occurred in 3 patients; three patients with chronic obstructive lung disease experienced CHF at the time of an exacerbation; one patient suffered acute pulmonary edema twice within a short period due to aortic regurgitation with coexistent aortic stenosis. Drugs prescribed to the 17 patients were: indomethacin (n=7), ibuprofen (n=5), diclofenac sodium (n=2), fenoprofen (n=1), naproxen (n=1), piroxicam (n=1).

In the remaining 5 cases the occurrence of CHF could be judged due to NSAID treatment: no other precipitant was found. Of these patients 4 had had indomethacin treatment and 1 patient diclofenac sodium. Details on these patients are listed in Table III*: the mean age was 77±4 years, there were 3 females and 2 males. The mean creatinine clearance was 76±15 ml/min. Four patients previously had no apparent heart disease; one patient with a moderately compromised cardiac status needed diuretic treatment with 40 mg furosemide daily. This patient had chronic atrial fibrillation; all other patients had a regular sinus rhythm at electrocardiography.

* Table III is presented at page 86 (reference 30)

TABLE II. DETAILS OF 13 PATIENTS WITH CHF SUSPECTED TO BE DUE TO THE USE OF NSAID, OBSERVED BY THE PHYSICIANS RETURNING THE QUESTIONNAIRE

Age/sex	NSAID, dosage mg/day	time interval	concomitant diuretic medication	findings of CHF	special remarks
81 F	oxyphenbutazone 3 x 100 p.o.	2 days	chlortalidone	pedal oedema, dyspnoea	no CHF known, hypertension
94 F	diclofenac sodium 3 x 25 p.o.	some days	furosemide	pedal oedema, rales	no CHF known
76 F	phenylbutazone indomethacin ibuprofen	some days		pedal oedema after all three NSAID's	CHF in the past
71 F	diclofenac sodium 3 x 50 p.o.	10 days	furosemide	pedal oedema	no CHF known
74 F	indomethacin 4 x 25 p.o.	12 days	furosemide	dyspnoea, rales, distended jugular veins, oedema	CHF in the past, concomitant pneumonia
85 F	naproxen supp. 5 x 500 p.o.	14 days	diuretics not specified	general oedema, rales	no CHF known, thyroid carcinoma with metastases
80 F	ibuprofen 3 x 400 p.o.	1 month		dyspnoea, rales	CHF in the past
82 M	naproxen 2 x 250 p.o.	1 month		dyspnoea, rales, distended jugular veins, oedema	sick sinus syndrome atherosclerosis, CHF in the past

63	F	ibuprofen 3 x 400 p.o.	1.5 month		acute pulmonary oedema	CHF in the past, atrial fibrillation
90	F	indomethacin supp. 50 mg once the other day	2 months	furosemide	pedal oedema, dyspnoea, rales	CHF in the past
89	F	ibuprofen 3 x 400 p.o.	3 months	diuretics not specified	pedal oedema, dyspnoea, rales	Chest X-ray: CHF, Weight gain 3 kg, CHF in the past
87	M	piroxicam 1 x 20 p.o.	5 months		dyspnoea. rales	CHF in the past, atrial fibrillation cor pulmonale
79	F	naproxen 3 x 250 p.o.	years	furosemide spironolacton		CHF in the past, atrial fibrillation

DISCUSSION

Study parts I and II are both retrospective analyses; inevitably the results are subject to bias due to methodological factors. In Study part I (the questionnaire to general practitioners and nursing home physicians) the information was obtained from a small group of responders. Approximately half the responders were familiar with CHF as a side effect of NSAID in the elderly.

In 9 of the 22 reported patients the event had taken place in the preceding 8 months. This may indicate a more common occurrence of NSAID-induced CHF if only the most recent patient was recalled by a few physicians, and other cases passed by unnoticed or were forgotten.

The subjects drawn from the hospital patient population (Study part II) probably do not represent a random sample of CHF patients in the community, but very likely form a group of elderly patients with more complex medical histories. Moreover collecting reliable and comprehensive data on drug intake often is difficult. It may be assumed that the number of patients within the hospital population listed with CHF and locomotor diseases was complete; however, the underreporting of NSAID medication in the patient records remains a problem, the more so since these drugs are commonly prescribed as analgesics.

The seven different NSAID administered to the patients of Study part I most likely represent the respondents' prescription preference among the numerous NSAID available today. In Study part II, NSAID-induced CHF is most often related to indomethacin treatment. This may be explained by the fact that indomethacin was the most prescribed NSAID for patients with rheumatoid arthritis in this hospital[10] at the time of the study.

Although drugs may differ in safety in this respect, CHF during NSAID treatment in the elderly may well be an inherent side effect of this class of drugs. It has been generally accepted that the NSAID, derivatives of a number of chemically unrelated compounds, have in common an inhibitory effect on cyclooxygenase. This is the key enzyme in the biosynthesis of prostaglandins and thromboxanes from

arachidonic acid. Most of the therapeutic actions and side effects of the various NSAID are similar and related to the inhibition of prostaglandin synthesis[11].

Two of the described cases of CHF during NSAID treatment in the elderly seem to be dose related. Drug toxicity may have precipitated acute pulmonary oedema in one female patient of the hospital population group, who exceeded the recommended daily dosage of 150 mg diclofenac sodium by taking 200 mg during 60 days. In the group of patients in Study part I, one took 2500 mg naproxen daily. In the elderly, half the adult dosage has been advised[12]. Apart from the existence of persons with a high risk characteristic it is possible that apparently healthy elderly individuals, due to age related factors per se, are more liable to suffer from a side effect, i.e. CHF during NSAID treatment.

Advanced age is a risk factor for acute renal deterioration caused by NSAID treatment[13,14]. The influence of NSAID on the kidney function is generally only modest and the majority of the pharmacodynamic effects observed during 3-4 days of NSAID use[15,16] disappear after prolonged administration[17-20]. No case of acute renal failure has been diagnosed in the patients with CHF in our study. However, data on the exact kidney function of the subjects reported by the physicians' questionnaire obviously cannot be given. The five patients of Study part II all had a normal or even above-average kidney function for their age at the time of diagnosis. Thus NSAID-induced renal failure cannot explain the solute retention in any of these patients.

Eight of the thirteen patients of the physicians' questionnaire and one of the patients in Study part II were known with CHF in the past. We do not have an estimate of the degree of heart failure for the majority of these. From the study of Dzau et al.[21] it is known that patients of all ages with severe heart failure and a serum sodium concentration below 135 mmol/l show a significant decrease in cardiac index and an increase in left ventricular end-diastolic pressure, mean arterial pressure and systemic vascular resistance when challenged with oral indomethacin. Further, some evidence is

available that prostaglandin metabolites and thromboxanes influence the coronary circulation of patients with heart disease[22,23], but at this moment there is no proof that NSAID exert a negative inotropic effect on the heart muscle, be it insufficient or not. It remains a possibility that in some of our patients with a compromised cardiac status, and thus critically dependent on prostaglandin-mediated vasodilation, the mechanism of CHF was the NSAID-induced imbalance of circulatory homoeostasis.

Finally four of the thirteen patients in Study part I and one of the five in Study part II had furosemide treatment. NSAID blunt the diuretic response to furosemide[5,24]. In these patients solute retention and congestive heart failure are readily explained by a decreased furosemide effect.

Peripheral oedema soon after the start of medication has been reported as an adverse effect of NSAID in 0-35% of the patients[25]. The responsible NSAID action possibly is an increase in chloride and sodium retention by the kidney at the site of the medullary segment of the thick ascending limb of Henle's loop[26]. This phenomenon obviously does not explain the precipitation of CHF in the majority of the elderly subjects described. One can only speculate about the fact that, or why patients with a previously unnoticed or clinically still undetectable degree of heart failure need an individually variable period of time before the symptoms of CHF ensue: the time interval between the start of drug administration and the occurrence of CHF varied between a few days and six months or more of continuous treatment with NSAID. The median time interval in the 13 patients of Study part I was one month, and that in the 22 patients of Study part II was 2 months. Therefore, no straightforward time-event relationship was abvious in the majority of the patients and this is one of the difficulties in assessing CHF as an adverse effect of NSAID treatment. A further approach to judge the apparent CHF as a possible side effect is to observe dechallenge: disappearance of symptoms after withdrawal of the suspected drug. This is not realistic in CHF, because, together with NSAID cessation, the introduction of other therapeutic interventions (e.g. bed rest,

dietary salt restriction, oxygen, diuretics and other medication) is appropriate. Rechallenge, re-administration of the suspected drug, often cannot be performed under identical conditions. Classic algorithms[27-29] for judging suspected adverse drug reactions use time-effect relationship, dechallenge and rechallenge as evidence. Assessment of NSAID-related CHF in the elderly patients of this study with such methods consequently results in a relatively low score of probability.

Our data confirm that CHF does occur, and presumably more often than the paucity of reports in literature would suggest, as a probable complication of NSAID treatment in the elderly. Patients with previous CHF or diuretic treatment are more at risk for NSAID-induced CHF, but the adverse effect also strikes elderly subjects with a hitherto uncompromised cardiac status. In contrast to earlier reports we did not find renal insufficiency in our patients. In some cases CHF is associated with a relative or absolute overdose.

Supposed that NSAID were causally involved in our patients, classic methods to evaluate side effects of drugs fail in this retrospective assessment for two main reasons: there is an unpredictable and sometimes long time interval between the start of treatment and the onset of symptoms, and the observation of dechallenge and rechallenge is often impossible. The retrospective nature of our study does not allow a firm conclusion either about the incidence of CHF as a complication due to NSAID treatment in the elderly or about the safety of one or more of the different NSAID in particular.

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AS A PROGNOSTIC FACTOR IN ACUTE PULMONARY EDEMA

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We read with interest the article by Goldberger et al. that was published in the March 1986 issue of the Archives[1]. In 106 admissions, the precipitant factor of acute pulmonary edema and the outcome of the illness have been studied by chart review and either telephone contact with the patients or analysis of questionnaires mailed to patients who could not be reached by telephone. Details of the patient's medical history and preadmission medication were presented, but therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) was not specifically mentioned. Occasionally, therapy with NSAIDs induces congestive heart failure by solute retention[2], or by blunting the diuretic response to furosemide therapy[3]. Today, NSAID therapy is administered widely to an impressive part of the elderly population[4,5].

We screened the records of 600 patients with congestive heart failure, consecutively admitted to the Department of Medicine of our hospital, in an attempt to find cases of congestive heart failure attributable to treatment with NSAIDs. Twenty-two patients were treated with NSAIDs at the moment of admission, because of previously diagnosed osteoarthritis (n=9), polymyalgia rheumatica (n=1), gout (n=1) and hypertrophic osteoarthropathy (n=1). The most likely cause or combination of causes to explain the occurrence of congestive heart failure could be determined in 17 of 22 patients, and these comprised the following: the onset of atrial fibrillation or flutter (25%), cessation or failure to comply with diuretic therapy (21%) or dietary salt restriction (14%), myocardial infarction (11%), progessive worsening of congestive cardiomyopathy (11%), lower airway infection in patients with chronic obstructive lung disease (11%), and valvular heart disease (7%). Concomitant use of therapy with NSAIDs had been initiated two or four weeks before the event (n=5) or had been going on for a much longer time (n=12).

Five cases of congestive heart failure were observed without any precipitant save the recent initiation of therapy with NSAIDs; details are listed in the Table. One patient (1) presented with the signs of acute pulmonary edema, and four other patients presented with lower leg edema, distended jugular veins, and weight gain. Only

one patient (4) had a moderately compromised cardiac status for which treatment with furosemide had been previously prescribed. All patients had normal kidney functions for their age at the onset of the event.

It must be noted here that indomethacin has been the most frequently prescribed NSAID in our hospital[6]. This can explain why one particular drug may have provoked the four cases of congestive heart failure due to therapy with NSAIDs, but it is possible that the various NSAID regimens differ in safety in this respect.

We, therefore, conclude that congestive heart failure as well as acute pulmonary edema can be precipitated by treatment with NSAIDs in elderly patients with an uncompromised cardiac status. Although NSAID-induced acute pulmonary edema is a rare event, we wonder if any of the patients in the study of Goldberger et al. could have experienced this side effect. If it is possible to withdraw the particular mode of therapy in such a case, we expect the prognosis of the patient to be ameliorated.

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TABLE. DETAILS OF FIVE CASES OF CONGESTIVE HEART FAILURE, PROBABLY DUE TO NSAID TREATMENT, OBSERVED IN A STUDY OF 600 ADMISSIONS*

Age/sex	Creatinine clearance ml/min (ml/s)	NSAID formulation	Dose mg/day	Start of NSAID treatment, days before congestive heart failure	Indication	Findings at admission	Body weight reduction after cessation of the NSAID	Survival, years
1/76/F	60 (1)	diclofenac sodium, sustained release	200	-60	rheumatoid arthritis	Acute pulmonary edema	3.4	> 2
2/80/F	100 (1.67)	indomethacin	75	-21	polymyalgia rheumatica	pedal edema, elevated jugular venous pressure	6.9	> 4.5
3/82/F	80 (1.33)	indomethacin, suppository	100	-80	rheumatoid arthritis	pedal edema, elevated jugular venous pressure	5.5	> 3
4/71/M	70 (1.17)	indomethacin	50	-60	osteoarthritis	pedeal edema, elevated jugular venous pressure	2.3	> 3.5
5/74/M	70 (1.17)	indomethacin, suppository	100	-3	osteoarthritis	pedal edema, elevated jugular venous pressure	unknown	1**

* assessed with the aid of a nomogram by the method of Siersbaek-Nielsen et al.[7]

NSAID indicates nonsteroidal anti-inflammatory drugs

**patient died of carcinoma of the pancreas

CHAPTER VIII

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

Non-steroidal anti-inflammatory drugs (NSAID) are the first choice in the symptomatic treatment of inflammatory joint diseases. Disease-associated changes in the function of body organs or in the composition of blood proteins, and individual patient characteristics alter drug disposition. The studies in this thesis concerned in particular the pharmacokinetics of the NSAID naproxen in relation to age and disease activity in patients with rheumatoid arthritis. Furthermore, a study was made of two adverse drug reactions both connected with the use of NSAID, either in the treatment of rheumatoid arthritis or for joint complaints in the aged patient.

Chapter I describes the drug studied, naproxen, and the implications of fluctuations in disease activity in patients with rheumatoid arthritis.

Chapter II gives the results of a pharmacokinetic study on eight patients with classic or definite rheumatoid arthritis and active polyarticular inflammation, studied during chronic treatment with 500 mg naproxen twice daily in comparison with results in healthy young volunteers.

The area under the concentration-time curve during one dose interval (AUC) of total naproxen was smaller in patients than in volunteers: 641±101 mgh/l versus 896±85 mgh/l; $p < 0.0001$. This corresponds with a lower mean serum drug concentration in patients during one dose interval. Protein-unbound drug concentrations were higher in patients, resulting in a larger $(AUC)_u$ than that of volunteers: 1.9±0.9 mgh/l versus 0.7±0.2 mgh/l; $p < 0.01$.

Total body clearance and apparent volume of distribution of the drug in patients increased in comparison with the volunteers. Naproxen elimination half-life did not change significantly. Volume of distribution and clearance were inversely correlated with individual serum albumin concentrations. In contrast with total naproxen kinetics, unbound clearance and volume of distribution were smaller in patients. These differences in drug pharmacokinetics are discussed as resulting from multiple causes: the age difference between

patients and volunteers, and the hypoalbuminaemia in patients (28±2 g/l versus 45±2 g/l in volunteers), associated with active rheumatoid arthritis or disease activity itself.
To study age and disease activity as factors determining naproxen pharmacokinetics the studies presented in the next three chapters were performed.

Chapter III describes the results of a pharmacokinetic study of naproxen 500 mg twice daily in six elderly patients (mean age 73±2.9 years) in comparison with those in eight healthy young volunteers (mean age 24±2.5 years). In the elderly patients the AUC of total naproxen was smaller; total body clearance and volume of distribution were increased. Unbound naproxen $(AUC)_u$ was larger in the elderly as compared with the young, together with a decrease in unbound clearance of the drug. The pharmacokinetic differences between the aged and the young may be explained by a lower serum albumin concentration (34±5 g/l versus 45±2 g/l in the young), together with a decrement in naproxen albumin binding affinity and a significant reduction in clearance of unbound drug in the elderly: 281±96 l/h versus 713±164 l/h; $p < 0.001$. The origin of the diminished binding affinity in the aged may be: either changes in the structure of the albumin molecule or the presence of endogenous inhibitors of binding. At this moment there is no clear answer to this question. Also one can only speculate about the nature of the diminished clearance of unbound naproxen in elderly patients. The advice to the clinician to start naproxen therapy in the aged at a low dosage and increase stepwise if necessary ("go low, go slow") is supported by the finding of higher free drug concentrations in the elderly.

Chapters IV and V present the results of a within-patient study of naproxen pharmacokinetics, comparing a period of active polyarticular inflammation with a period of improvement. The patients were receiving chronic treatment with naproxen 500 mg twice daily. Total naproxen concentrations were significantly lower in active disease, together with a significantly larger volume of distribution and

clearance. Peak unbound drug concentrations were 29±19% ($p < 0.05$) lower at the time of improvement, but trough concentrations and concentrations of unbound drug measured in both periods after the dose interval up to60 hours were indistinguishable. The unbound naproxen clearance was smaller in the period of active disease: 390±277 l/h in comparison with improvement: 488±343 l/h; $p < 0.05$. In some patients a difference in albumin binding affinity existed; at this moment we can give no final explanation of the cause of this finding, nor judge its clinical implications. In any case disease activity in patients with rheumatoid arthritis alters naproxen disposition. Hypoalbuminaemia associated with active polyarticular inflammation (mean serum albumin 30±4 g/l, versus 41±2 g/l in improvement) explains a larger volume of distribution and clearance of the drug. A calculation of the unbound naproxen pharmacokinetics revealed a decrement in clearance at the time of active disease, possibly as a consequence of reduced hepatic uptake from plasma or a hampered metabolism of the drug.

The clinical implications are:

- a possible beneficial effect due to higher unbound naproxen concentrations in patients with active polyarticular inflammation, assuming that unbound drug levels correlate with therapeutic effect; and the other side of the coin:
- a possible higher frequency of adverse drug reactions as a consequence of the higher unbound drug levels in patients with active disease.

The rationale for the study described in Chapter VI, the assessment of gastrointestinal blood loss associated with NSAID treatment using ^{51}Cr-labelled erythrocytes, was the observation of higher unbound naproxen concentrations in patients with active rheumatoid inflammation. In view of these higher unbound drug levels one might expect an increased pharmacological effect, and thus a relationship between the amount of gastrointestinal damage, measured as faecal ^{51}Cr loss, and the unbound naproxen concentration in patients with active rheumatoid arthritis. However, no significant correlation was

found, either with unbound or total drug concentrations, or duration of naproxen therapy, or degree of disease activity in individual patients. The results of faecal ^{51}Cr loss in our nine patients were quite similar to earlier data on volunteers and out-patients with rheumatoid arthritis. We concluded that it was not useful to extend the number of participating patients or to compare the gastro-intestinal ^{51}Cr loss in these patients with assessments in healthy volunteers taking naproxen.
Furthermore, the follow-up of these patients after the study period illustrates that absence of a more than expected ^{51}Cr loss has no predictive value for ulcerogenesis.

Chapter VII describes observations on a suspected adverse drug reaction; i.e. congestive heart failure due to NSAID treatment in the elderly. Twenty-two patients were reported by means of a questionnaire sent to 243 practicing physicians; 48% of the respondents expressed awareness of the possibility of congestive heart failure as a NSAID-related side effect. In the University Hospital St Radboud, the medical records of 600 patients with congestive heart failure revealed five cases possibly attributable to NSAID therapy. The probability of an unwanted effect to be associated with the use of a drug, and thus to be an adverse drug reaction, can be assessed with standardized decision aids (algorithms). The nature of a retrospective study makes manoeuvres in individual patients impossible, and sometimes files are incomplete or important observations have not been made. Therefore, these algorithms fail to reach a high level of probability in the described groups of patients. Our results confirm that congestive heart failure does occur as an adverse drug reaction to NSAID therapy in the elderly. The incidence of this adverse drug reaction, or the identification of high-risk individuals, could not be derived from these data.

SAMENVATTING EN CONCLUSIES

Niet-steroide anti-inflammatoire geneesmiddelen (NSAID) zijn de eerste keus bij de symptomatische behandeling van gewrichtsontstekingen bij ziekten van het bewegingsapparaat. Naast individuele, patiëntgebonden eigenschappen, beïnvloeden met ziekte samenhangende veranderingen in de functie van organen, of in de samenstelling van bloedeiwitten de lotgevallen van een geneesmiddel in het lichaam. De onderzoekingen in dit proefschrift betroffen in het bijzonder de farmacokinetiek van het NSAID naproxen in verband met leeftijd en ziekte-activiteit van patiënten met rheumatoïde arthritis. Verder werden twee bijwerkingen bestudeerd, die samenhangen met het gebruik van NSAID bij de behandeling van rheumatoïde arthritis of met het gebruik wegens gewrichtsklachten bij bejaarde patiënten.
Hoofdstuk I beschrijft het geneesmiddel naproxen en de betekenis van de wisselingen in ziekte-activiteit bij patiënten met rheumatoïde arthritis.

Hoofdstuk II toont de resultaten van een farmacokinetische studie verricht tijdens chronische behandeling met tweemaal daags 500 mg naproxen bij acht patiënten met klassieke of zekere rheumatoïde arthritis en een actieve gewrichtsontsteking in vergelijking met gezonde jonge vrijwilligers. Het oppervlak onder de concentratie-tijdcurve tijdens één dosisinterval (AUC) voor het totale naproxen bleek kleiner bij patiënten dan bij vrijwilligers: 641±101 mgh/l tegen 896±85 mgh/l; $p < 0,0001$. Dit behelsde dus een lager gemiddeld gehalte aan geneesmiddel in het serum tijdens het dosisinterval bij patiënten. Het niet-eiwitgebonden geneesmiddel-gehalte was hoger bij de patiënten, met als gevolg een grotere $(AUC)_u$ dan die van vrijwilligers: 1,9±0,9 mgh/l tegen 0,7±0,2 mgh/l; $p < 0,01$. De totale lichaamsklaring en het schijnbaar verdelingsvolume van de stof was bij patiënten toegenomen in vergelijking met vrijwilligers. De eliminatie halfwaardetijd was niet significant verschillend. Het verdelingsvolume en de klaring toonden een negatieve correlatie met het individuele serum albumine-gehalte. In tegenstelling tot de kinetiek voor het totale naproxen waren de vrije klaring en het ver-

delingsvolume van de niet-eiwitgebonden stof kleiner bij de patiënten. Deze verschillen in farmacokinetiek lijken meerdere oorzaken te hebben, die in de discussie worden besproken: het verschil in leeftijd tussen patiënten en vrijwilligers, de hypalbuminemie bij patiënten (28±2 g/l tegen 45±2 g/l bij vrijwilligers) waarmee actieve rheumatoïde arthritis gepaard gaat, of de ziekte-activiteit zelf.
Om leeftijd en ziekte-activiteit als de bepalende factoren voor naproxen-kinetiek te bestuderen werden de onderzoekingen, die in de hierop volgende drie hoofdstukken zijn uiteengezet, ondernomen.

In Hoofdstuk III worden de resultaten beschreven van een farmacokinetische studie met tweemaal daags 500 mg naproxen bij zes bejaarde patiënten (gemiddelde leeftijd 73±2,9 jaar) in vergelijking met die van acht jonge gezonde vrijwilligers (gemiddelde leeftijd 24±2,5 jaar). Bij de bejaarde patiënten was de AUC voor totaal naproxen kleiner, de totale lichaamsklaring en het verdelingsvolume waren groter. De niet-eiwitgebonden $(AUC)_u$ van naproxen was groter bij de ouderen in vergelijking met de jongeren, samen met een verminderde klaring van het vrije naproxen. De verschillen in farmacokinetiek tussen ouderen en jongeren kunnen worden verklaard uit een lager serum albuminegehalte (34±5 g/l tegen 45±2 g/l bij de jongeren), samen met een verminderde bindingsaffiniteit van naproxen aan albumine en een significant kleinere klaring (281±96 l/h tegen 713±164 l/h; $p < 0,001$) van de vrije stof bij de bejaarden. De verminderde bindingsaffiniteit bij ouderen kan voortkomen uit: ofwel veranderingen in de structuur van het albumine molecule, ofwel de aanwezigheid van lichaamseigen stoffen die de binding hinderen. Op dit moment bestaat op deze vraag geen sluitend antwoord. Ook kan men slechts speculeren over de oorzaak van de verminderde klaring van niet-eiwitgebonden naproxen bij oudere mensen. Het advies aan de klinicus om naproxen-therapie bij ouderen met een lage dosis te beginnen en de dosis stapsgewijze te verhogen wanneer nodig "go low, go slow", wordt door de bevinding van hogere vrije geneesmiddelconcentraties bij bejaarden gesteund.

In Hoofdstuk IV en Hoofdstuk V worden de resultaten getoond van een farmacokinetische studie, waarbij dezelfde patiënten met rheumatoïde arthritis werden onderzocht tijdens een periode van actieve gewrichtsontsteking en een periode van vermindering of afwezigheid hiervan. De patiënten gebruikten chronisch tweemaal daags 500 mg naproxen. Tijdens de actieve ziekte-periode waren de totale naproxen-concentraties significant lager, samen met een groter verdelings-volume en klaring. De hoogst gemeten niet-eiwitgebonden concentraties waren 29±19% lager ($p < 0,05$) op het moment dat de ziekte in een rustige fase verkeerde, maar de dalspiegels en de spiegels van het niet-eiwitgebonden naproxen die in beide perioden werden bepaald na het dosisinterval tot 60 uur waren niet van elkaar verschillend. De klaring van niet-eiwitgebonden naproxen was kleiner tijdens de actieve ziekteperiode: 390±277 l/h, in vergelijking met de rustige periode: 488±343 l/h; $p < 0,05$. Er bestond bij enkele patiënten een veranderde bindingsactiviteit van naproxen aan albumine; hiervoor is geen goede verklaring voorhanden, evenmin er een oordeel over de klinische betekenis ervan kan worden gegeven. In ieder geval beïnvloedt de ziekte-activiteit de lotgevallen van naproxen in het lichaam van de patiënt met rheumatoïde arthritis. De periode van actieve ziekte gaat gepaard met hypalbuminemie (serum albumine 30±4 g/l tegen 41±2 g/l in de rustige periode), wat het grotere verdelingsvolume en klaring van naproxen verklaart. Berekening van de niet-eiwitgebonden farmacokinetiek van naproxen openbaarde een verminderde klaring tijdens de actieve ziekteperiode, mogelijk als gevolg van een verminderde opname door de lever uit het plasma of ten gevolge van een gestoord metabolisme van de stof. De klinische consequenties zijn:

- een mogelijk gunstig effect ten gevolge van hogere niet-eiwit-gebonden naproxen-concentraties, aangenomen dat deze correleren met het therapeutisch effect, bij patiënten met actieve rheumatoïde arthritis en
- een mogelijk tevens grotere frequentie van bijwerkingen van het geneesmiddel, eveneens als gevolg van de hogere niet-eiwitgebonden concentratie bij patiënten met actieve gewrichtsontsteking.

De achtergrond van het in Hoofdstuk VI beschreven onderzoek, de meting van gastrointestinaal bloedverlies ten gevolge van NSAID-gebruik met behulp van ^{51}Cr-gelabelde erythrocyten, was de bevinding van de hogere niet-eiwitgebonden naproxen-concentraties bij patiënten met actieve rheumatoïde arthritis. Men zou op grond van deze hogere vrije geneesmiddel-concentraties een krachtiger farmacologisch effect kunnen verwachten, en dus een verband tussen de schade aan het maag-darmkanaal, gemeten als ^{51}Cr verlies, en de niet-eiwitgebonden concentratie van naproxen bij patiënten met actieve gewrichtsontsteking. Er werd echter geen significant verband gevonden, noch met vrij of totaal naproxen, noch met de duur van de naproxen-therapie, noch met de graad van ziekte-activiteit bij individuele patiënten. Het verlies van ^{51}Cr bij onze negen patiënten was geheel overeenkomstig met dat in studies verricht bij vrijwilligers of niet in de kliniek opgenomen patiënten met rheumatoïde arthritis. Wij concludeerden hieruit dat het niet zinvol was het aantal patiënten in de studie uit te breiden, of hun ^{51}Cr uitscheiding te vergelijken met metingen bij vrijwilligers tijdens naproxen-gebruik. Verder liet het vervolg van de patiënten na de studie zien, dat het ontbreken van een meer dan te verwachten faecaal ^{51}Cr verlies geen voorspellende waarde heeft voor het al dan niet ontstaan van een ulcus.

Hoofdstuk VII beschrijft het onderzoek naar een vermoede bijwerking van NSAID bij bejaarden, te weten decompensatio cordis. Uit een enquête verzonden naar 243 artsen verkregen we gegevens over 22 patiënten bij wie verdenking op de bijwerking bestond; van de respondenten meldde 48% op de hoogte te zijn van de bijwerking decompensatio cordis ten gevolge van NSAID-therapie bij bejaarden.
In de medische dossiers van 600 patiënten met decompensatio cordis in het Sint Radboud Ziekenhuis werden 5 patiënten gevonden, waarvan de decompensatie mogelijk tot waarschijnlijk aan het gebruik van NSAID te wijten was. De waarschijnlijkheid waarmee een ongewenst effect samenhangt met het gebruik van een geneesmiddel, en derhalve een bijwerking is, kan worden geschat met gebruikmaking van gestan-

daardiseerde beslissingstabellen (algoritmen). De aard van een retrospectief onderzoek verhindert de uitvoering van onderzoek bij de patiënt zelf, soms blijken gegevens incompleet of zijn belangrijke waarnemingen niet verricht. In de beschreven patiëntengroepen komen de bijwerkingen-algoritmen juist hierom niet tot een grote waarschijnlijkheid voor de vermoede bijwerking. De resultaten van het onderzoek bevestigen dat decompensatio cordis ten gevolge van het gebruik van NSAID bij bejaarden voorkomt. Uit deze gegevens konden noch de incidentie van de bijwerking, noch de risicofactoren bij individuele patiënten hiervoor, worden afgeleid.

DANKWOORD

Bij de voltooiing van dit proefschrift wil ik allen, die op enigerlei wijze hebben bijgedragen aan de totstandkoming ervan, bedanken. Dit geldt in het bijzonder voor de patiënten die, niet opziend tegen verstoring van de dagelijkse gang van zaken, hun welwillende medewerking verleenden aan de studies. De gastvrije ontvangst, hetzij aan het ziek(enhuis)bed, dan wel voor een herhaald onderzoek bij de patiënt(e) aan huis, was stimulerend.

Ook moet hier worden vermeld de bijdrage van de studenten die als proefpersonen participeerden en zich met grote zorgvuldigheid van hun taak kweten.

De medische staven van de onderafdeling Reumatologie van de Kliniek voor Inwendige Ziekten en van de afdeling Reumatologie van de Sint-Maartenskliniek te Nijmegen nodigden mij uit aanwezig te zijn op hun wekelijkse patiëntenbesprekingen. Dit bood de mogelijkheid tot vlot overleg met de behandelend specialist aangaande patiënten die, òf voor de studie benaderd zouden kunnen worden, òf aan het onderzoek reeds deelnamen.

De verpleegkundigen van bovengenoemde reumatologische afdelingen bleken immer bereid te hulp te schieten, daar waar extra zorg nodig was om het verzamelen van studiematerialen te vervolmaken.

Het Laboratorium voor Klinische Chemie van de Kliniek voor Inwendige Ziekten (hoofd: dr J.C.M. Hafkenscheid) verrichtte de in aanmerking komende bepalingen in bloed- en urinemonsters.

Op het laboratorium van de werkgroep Klinische Farmacologie en Farmacokinetiek werkte Y. Tan met grote nauwgezetheid aan de bepalingen van naproxen in lichaamsvloeistoffen. Aan zijn deskundigheid en inzet op het gebied van evenwichtsdialyse is het te danken, dat niet-eiwitgebonden naproxen met reproduceerbare precisie kon worden gemeten.

Het laboratorium van de afdeling Reumatologie van de Rijksuniversiteit Groningen (hoofd: prof.dr M.H. van Rijswijk) dank ik voor de uitvoering van de C-reactive protein-bepalingen.

Op de afdeling Nucleaire Geneeskunde (hoofd: dr F.H.M. Corstens) verrichtten W.J.M. van den Broek en A.C. Felten met zorgvuldigheid de

labeling van erythrocyten met ^{51}Cr en daaropvolgend de meting van bloedverlies uit het maag-darmkanaal. Drs W.C.A.M. Buijs dank ik voor de zorg besteed aan de berekening van de stralenbelasting.
De studie van de bijwerking decompensatio cordis bij bejaarde NSAID-gebruikers maakte de hulp van respectievelijk de Stichting Medische Registratie (hoofd: G. Tummers, ing) en de medewerkers van het Medische Archief van de Kliniek voor Inwendige Ziekten onontbeerlijk. Ook dank ik de respondenten van de enquête voor hun mededelingen.
Hat in dit proefschrift gepresenteerde mocht onderwerp zijn van vruchtbare discussies met de collegae C.F.M. Rosmalen, prof.dr C. van Weel en de staf van het Nijmeegs Universitair Huisartseninstituut; voorts met dr F.H.M. Corstens, dr P.A.F. Jansen en R.H.B. Meyboom, medeauteurs van respectievelijke artikelen. P.C. Eenhoorn, farmaceut en gewaardeerd ambassadeur van Sarva Syntex Nederland, bleek een opbouwend kritisch begeleider.
Th. van Winsen te Amsterdam corrigeerde de Engelse taal.
De medewerkers van de Medische Bibliotheek (hoofd: drs S. Bakker) waren behulpzaam bij het verzamelen van literatuur.
Tekeningen in dit proefschrift werden vervaardigd en gefotografeerd door medewerkers van de afdeling Medische Illustratie (hoofd: F. de Jonge).
De omslag van het proefschrift werd verzorgd door G. Peeters van de afdeling Reprografie; hier werd ook het drukwerk verricht.
Voor secretariële werkzaamheden ben ik dank verschuldigd aan T. de Jong (Sarva Syntex Nederland, Rijswijk), A. van Loon (Nucleaire Geneeskunde) en K.E. van Horssen-Hamerslag (Reumatologie). G.C.A. Wessel-Hoogstraaten verzorgde met grote toewijding het merendeel van de manuscripten van de artikelen, bracht de hoofdstukken van dit proefschrift op tekstverwerker, corrigeerde de tekst en verwerkte wijzigingen; gaf tenslotte de finishing touch aan het geheel.

CURRICULUM VITAE

De schrijver van dit proefschrift werd op 28 september 1953 geboren te Nieuw-Ginneken. Hij behaalde in 1972 aan het Onze Lieve Vrouwe Lyceum te Breda het eindexamen Hogereburgerschool B en studeerde vervolgens Geneeskunde aan de Katholieke Universiteit te Nijmegen. Het doctoraal examen Geneeskunde werd afgelegd in 1977 en het artsexamen in september 1979.

Tijdens het vervullen van de militaire dienstplicht werd hij, na de basistraining, als reserve-eerste-luitenant-arts gedetacheerd bij de afdeling Bloedziekten van het St Radboud Ziekenhuis te Nijmegen (hoofd: prof.dr C. Haanen). Hij participeerde in onderzoek naar de ontwikkeling van methoden tot zuivering en preservatie van hematopoëtische progenitorcellen.

In juni 1981 werd aangevangen met de opleiding tot internist in het St Radboud Ziekenhuis (opleider: prof.dr A. van 't Laar), welke naar verwachting zal worden voltooid in september 1987.

Van oktober 1984 tot april 1987 was hij werkzaam binnen de werkgroep Klinische Farmacologie en Farmacokinetiek (hoofd: prof.dr F.W.J. Gribnau) van het Laboratorium Farmacologie (hoofd: prof.dr C.A.M. van Ginneken) en de onderafdeling Reumatologie (hoofd: prof.dr L.B.A. van de Putte) van de Kliniek voor Inwendige Ziekten van het St Radboud Ziekenhuis. In deze periode is het onderzoek verricht dat de basis vormde voor dit proefschrift.

STELLINGEN

1. Bij een sterk eiwitgebonden geneesmiddel kan zich de paradoxale situatie voordoen, dat een toegenomen totale lichaamsklaring gepaard gaat met een verminderde plasmaklaring van de niet-eiwitgebonden stof; dit resulteert in hogere niet-eiwitgebonden concentraties.
dit proefschrift.

2. Rheumatoide arthritis beinvloedt klaring en verdelingsvolume van totaal en niet-eiwitgebonden naproxen; dit resulteert bij patienten met een hypoalbuminaemie ten gevolge van aktieve ziekte in lagere totale en hogere niet-eiwitgebonden serumconcentraties gedurende het dosisinterval.
dit proefschrift.

3. Het advies naproxen therapie bij bejaarde patienten met een lage dosis aan te vangen en slechts zo nodig te verhogen, vindt extra rechtvaardiging in de te verwachten hogere, niet-eiwitgebonden naproxen serumconcentraties.
dit proefschrift.

4. Bij patienten met rheumatoide arthritis, die met naproxen worden behandeld, bestaat geen bewijs voor de veronderstelling als zou het verlies van radioaktiviteit met de faeces uit ^{51}Cr-gelabelde erythrocyten gerelateerd zijn aan de serumspiegels van het geneesmiddel of de ziekteaktiviteit van rheumatoide arthritis.
dit proefschrift.

5. Het verdient overweging het waarnemen, duiden en vastleggen van bijwerkingen van geneesmiddelen op te nemen als onderwerp in het basisonderwijs interne geneeskunde; dit mede in het licht van het vrijwel ontbreken van meldingen van bijwerkingen uit de academische klinieken.
Meyboom R.H.B. Het melden van bijwerkingen van geneesmiddelen in Nederland. Ned Tijdschr Geneeskd 1986; 130: 1879-1883.
Faich G.A. Adverse-drug-reaction monitoring. New Engl J Med 1986; 314: 1589-1592.

6. De registratie van geneesmiddelen moet periodiek worden getoetst aan de stand van de wetenschap; aanpassingen in de bijsluitertekst zouden de voorschrijvende arts op duidelijke wijze kenbaar moeten worden gemaakt.

Herxheimer A. Basic information that prescribers are not getting about drugs. Lancet 1987; 1: 31-32.

7. De klinisch-therapeutische beoordeling van geneesmiddelen voor registratie is gebaat bij de inbreng van medici, die werkzaam zijn in de klinische praktijk.

8. Bij stabiele inspanningsafhankelijke angina pectoris, die onvoldoende reageert op continue transcutane nitroglycerine toediening (Trasiderm-Nitro®), kan verlaging van de dosis per dag door intermitterende toediening zinvoller zijn dan het in de Nederlandse bijsluiter gegeven advies tot dosisverhoging.

Cowan D., Bourke J., Reid D.S. & Julian D.G. Tolerance to glyceryl trinitrate patches: prevention by intermittent dosing. Br Med J 1987; 294: 544-545.

9. De oogboldrukverlagende werking bij glaucoom door 1-timolol maleaat (Timoptol®) berust niet op de ß-blokkerende eigenschappen van dit middel.

Keates E.U. & Stone R. The effect of d-timolol on intraocular pressure in patients with ocular hypertension. Am J Ophtalmol 1984; 98: 73-78.
Leopold I.H & Duzman E. Observations on the pharmacology of glaucoma. Ann Rev Pharmacol Toxicol 1986; 26: 401-426.

10. De conclusies van Abernathy et al. aangaande de werking en kinetiek van d,l-verapamil (Isoptin®) zijn van weinig waarde, daar geheel voorbij is gegaan aan het verschil in farmacologisch effect tussen beide stereoisomeren en het stereospecifiek metabolisme.

Abernathy D.R., Schwarz J.B., Todd E.L., Luchi R. & Snow E. Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients. Ann Intern Med 1986; 105: 329 336.
Echizen H., Vogelgesang B. & Eichelbaum M. Effects of d,l-verapamil on atrioventricular conduction in relation to its stereoselective first-pass metabolism. Clin Pharmacol Ther 1985; 38: 71-76.

11. Het is nuttig, bij de bestudering van het Medical Knowledge Self-Assessment Program van het American College of Physicians, in gedachten te houden, dat soms de gegeven antwoorden Noord-Amerikaanse antwoorden op Noord-Amerikaanse problemen zijn.

12. In een enkel geval kan met één patient een "randomised clinical trial" worden uitgevoerd.

    McLeod R.S., Cohen Z., Taylor D.W. & Cullen J.B. Single-patient randomised clinical trial.
    Lancet 1986; i: 726-728.

13. Het als uniek voor het NSAID suprofen beschreven bijwerkingensyndroom, bestaande uit een acute reversibele nierfunktiestoornis met proteinurie en pijn in de flanken, lijkt zijn enigheid eerder te ontlenen aan de lijders (voornamelijk Noord-Amerikanen, werkzaam in de gezondheidszorg) dan aan de verschijnselen op zich.

    Hart D., Ward M. & Lifschitz M.D. Suprofen-related nephrotoxicity.
    Ann Intern Med 1987; 106: 235-238.

14. Eén voordeel, voortvloeiend uit de door het Ministerie van WVC aangekondigde beeindiging van de gratis toezending van het "Geneesmiddelenbulletin", is de nu verworven zekere kennis dat 6000 artsen in Nederland bereid zijn financieel bij te dragen in hun onafhankelijke geneesmiddelen informatie.
    Een opiniepeiler zou tegen aanzienlijke kosten een veel minder betrouwbaar antwoord op deze vraag hebben kunnen geven.

Nijmegen, 22 mei 1987 Frank van den Ouweland.